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10-50

Requestor's Name: Dwayne C Jones

Serial Number: 08/833,842

Date: 01 OCT 97 Phone: 308-4634 Art Unit: 1205

Search Topic:

Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevent citations, authors, keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevent claim(s).

Please search claim 1 and 15 and 16

examples of the diseases are found in claim 3

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27-

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Total time:

Number of Searches:

Number of Databases:

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Bibliographic

STN

APS

Geninfo

SDC

Other

PTO-1590 (9-90)

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     (FILE 'REGISTRY' ENTERED AT 10:37:46 ON 02 OCT 1997)
                DEL HIS Y
                E HMG COA/CN
L1              1 S E4
                E L-ARGININE/CN
L2              1 S E3
                E NO SYNTHASE/CN
L3              1 S E3
                E HMG COA REDUCTASE/CN
L4              2 S E6
                E LOVASTATIN/CN
L5              1 S E3
                E PRAVASTATIN/CN
                E SIMVASTATIN/CN
L6              1 S E3
                E FLUVASTATIN/CN
L7              1 S E3
                E DALVASTATIN/CN
L8              1 S E3
                E DOMPACTIN/CN
                E COMPACTIN/CN
L9              2 S E3
                E HR-780/CN
                E HR 780/CN
L10             1 S E3
                E MBY 22089/CN
                E BMY 22089/CN
L11             1 S E3
                E BMY 22566/CN
L12             1 S E3
                E SQ 33600/CN
L13             1 S E3
                E GR 95030/CN
L14             1 S E3
                E CI 981/CN
L15             1 S E3
L16            12 S L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13

     FILE 'HCAPLUS' ENTERED AT 10:43:11 ON 02 OCT 1997
L17         33396 S L2 OR ARGININE
L18          3325 S L4 OR HMG COA REDUCTASE#
L19             6 S L17 AND L18
L20          5773 S L3 OR (NO OR NITRIC OXIDE) (W) SYNTHASE#
L21          1784 S L16 OR LOVASTATIN OR PRAVASTATIN OR SIMVASTATIN OR FLUV
L22            15 S SQ 33600 OR SQ 33 600 OR GR (W) (95030 OR 95 030 ) OR C
L23          1785 S L22 OR L21
L24            11 S L17 AND L23
L25           905 S L20 AND L17
L26            40 S L20 (L) AGONIST#
L27            10 S L26 AND L25
L28         82699 S (HEART OR RENAL OR KIDNEY OR BRAIN ) (L) (DISEASE# OR D
L29         27698 S ANTIHYPERTENSIVE? OR CARDIOVASCULAR AGENT# OR VASODILAT
L30            40 S L25 AND L29
L31            51 S L25 AND L28
L32            86 S L30 OR L31
L33            13 S L32 AND (TREAT? OR THERAP?)
L34            21 S L24 OR L27
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L35 13 S L33 NOT L34
L36 0 S L34 AND (L28 OR L29)
L37 0 S L34 AND (VASOCONSTRIC? OR VASORELAX? OR RENOVASCULAR OR

=> d .ca l19 1-6;d .ca l35 1-13

L19 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 1997 ACS
AN 1996:497325 HCAPLUS
DN 125:151167
TI A controlled release drug delivery device comprising two-layered core and coating
IN Rork, Gerald S.; Pipkin, James D.
PA Merck and Co., Inc., USA
SO PCT Int. Appl., 33 PP.
CODEN: PIXXD2
PI WO 9619201 A1 960627
DS W: AL, AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, US, UZ, VN
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 95-US16530 951218
PRAI US 94-363451 941222
DT Patent
LA English
AB A device disclosed for the controlled delivery of a beneficial agent consisting of (1) a core comprising at least two layers, wherein at least one layer comprises a beneficial agent and a polymer which forms microscopic gel beads upon hydration and at least one layer which comprises a polymer which forms microscopic gel beads upon hydration; and (2) an impermeable, insol. coating which adheres to and surrounds the core and contains apertures which provide an area for the hydration and release of the microscopic gel beads. A two-layered core contained lovastatin (I) 40, Carbopol 974P 16, trisodium citrate 32, and lactose 16 mg/layer in the first layer and Avicel PH101 20, Carbopol 974P 8, trisodium citrate 16, and lactose 8 mg/layer in the second layer. The cores were coated with a soln. of cellulose acetate butyrate 20, and triethylcitrate 3 parts in a soln. of acetone:ethanol (3:1) and sprayed onto the cores to a thickness of 100.mu.m and two holes were drilled in the face of the device. The release profile of the two layer device were significantly improved over the single compn. core, in that the last 20% of I was released at a more const. rate and greater than 95% of the I content was released in <20 h.
IT **74-79-3**, **Arginine**, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(controlled release drug delivery device comprising two-layered core and coating)
IT **37250-24-1**, **HMG CoA reductase**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors, controlled release drug delivery device comprising two-layered core and coating)
IC ICM A61K009-24
ICS A61K009-32; A61K009-36
CC 63-6 (Pharmaceuticals)
IT 57-50-1D, Sucrose, allyl ethers **74-79-3**, **Arginine**
, biological studies 77-93-0, Triethyl citrate 115-77-5D, Pentaerythritol, allyl ethers 144-55-8, Sodium bicarbonate, biological studies 497-19-8, Sodium carbonate, biological studies

994-36-5, Sodium citrate 9002-86-2, Polyvinyl chloride
9004-35-7, Cellulose acetate 9004-36-8, Cellulose acetate butyrate
9004-57-3, Ethyl cellulose 9033-79-8 21829-25-4, Nifedipine
75330-75-5, Lovastatin 81093-37-0, Pravastatin 151687-96-6,
Carbopol 974P 179953-94-7
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(controlled release drug delivery device comprising two-layered core and coating)

IT **37250-24-1, HMG CoA reductase**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors, controlled release drug delivery device comprising two-layered core and coating)

L19 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 1997 ACS
AN 1996:79992 HCAPLUS
DN 124:136078
TI Cellular signaling and proliferative action of **arginine** vasopressin in glomerular mesangial cells
AU Ishikawa, San-e; Okada, Koji; Saito, Toshikazu
CS Department Medicine, Jichi Medical School, Tochigi, Japan
SO Int. Congr. Ser. (1995), 1098(Neurohypophysis: Recent Progress of Vasopressin and Oxytocin Research), 583-90
CODEN: EXMDA4; ISSN: 0531-5131
DT Journal
LA English
AB The present study was undertaken to det. whether low d. lipoprotein (LDL) and an inhibitor of 3-hydroxy-3-methylglutaryl CoA (HMG Co A) reductase affect the cellular action of arginine vasopressin (AVP) in cultured rat glomerular mesangial cells. LDL accelerated the cellular signaling and proliferative action of AVP. An effect was mediated through an increase in the breakdown of phosphatidylinositol, without any alteration in AVP V1-receptor binding. Such an augmentation by LDL was not obtained in cells derived from spontaneously hypertensive rats, because the genetic factor of an increase in AVP receptor capacity was much stronger than such an environmental factor as LDL. In contrast, an inhibitor of HMG Co A reductase, simvastatin, decelerated the cellular signaling and proliferative action of AVP. Since a pathway of cholesterol synthesis is not present in glomerular mesangial cells and mevalonate is involved in ras protein, the nonsterol pathway may play a crucial role in the action of G protein to activate cellular signal transduction of AVP in glomerular mesangial cells.
IT **9028-35-7**, 3-Hydroxy-3-methylglutaryl CoA reductase
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(inhibitor, deceleration of AVP effect on signaling and proliferation in glomerular mesangium)
CC 2-5 (Mammalian Hormones)
IT 113-79-1, **Arginine** vasopressin
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(effect on signaling and proliferation in glomerular mesangium)
IT **9028-35-7**, 3-Hydroxy-3-methylglutaryl CoA reductase
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(inhibitor, deceleration of AVP effect on signaling and proliferation in glomerular mesangium)

L19 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 1997 ACS

AN 1995:516036 HCAPLUS
DN 122:256686
TI Simvastatin inhibits the cellular signaling and proliferative action of **arginine** vasopressin in cultured rat glomerular mesangial cells
AU Ishikawa, San-E; Kawasumi, Midori; Saito, Toshikazu
CS Dep. Med., Jichi Med. Sch., Tochigi, 329-04, Japan
SO Endocrinology (1995), 136(5), 1954-61
CODEN: ENDOAO; ISSN: 0013-7227
DT Journal
LA English
AB The present study was undertaken to det. whether an inhibitor of 3-hydroxy-3-methylglutaryl CoA (HMG CoA) reductase, simvastatin, modulates the cellular action of arginine vasopressin (AVP) in the cultured rat glomerular mesangial cells. AVP increases cellular free calcium ([Ca2+]i) in a dose-dependent manner. The 1.times.10-7 M, AVP-mobilized [Ca2-]i was significantly reduced in the cells pretreated with 1.times.10-6 M simvastatin. AVP produced a biphasic change in cellular pH, namely, an early acidification followed by a sustained alkalinization, and the AVP-induced cellular alkalinization disappeared after exposing to simvastatin. At 1.times.10-7 M AVP activated mitogen-activated protein (MAP) kinase from 15.5-30.4 pmol/mg protein, an effect significantly less in the presence of simvastatin. Also, 1.times.10-7 M AVP significantly increased [3H]thymidine incorporation by 1.6-fold, and its incorporation was totally diminished in cells pretreated with simvastatin. The AVP-induced [Ca2+]i mobilization and MAP kinase activation were totally restored when cells were preexposed to a mixt. of mevalonate and simvastatin. [3H]AVP receptor binding was not affected by the simvastatin treatment. At 1.times.10-7 M, AVP increased inositol trisphosphate prodn. by 1.8-fold, which was significantly reduced by the presence of simvastatin. These results may indicate that nonsterol pathway plays a crucial role in the cellular action of AVP to produce cell growth of glomerular mesangium.
IT **9028-35-7, HMG-CoA reductase**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(simvastatin inhibition of cellular signaling and proliferative action of vasopressin in cultured glomerular mesangial cells)
CC 2-5 (Mammalian Hormones)
IT 113-79-1, **Arginine** vasopressin
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(simvastatin inhibition of cellular signaling and proliferative action of vasopressin in cultured glomerular mesangial cells)
IT 150-97-0, Mevalonic acid 7440-70-2, Calcium, biological studies **9028-35-7, HMG-CoA reductase** 142243-02-5, MAP kinase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(simvastatin inhibition of cellular signaling and proliferative action of vasopressin in cultured glomerular mesangial cells)

L19 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 1997 ACS
AN 1994:235834 HCAPLUS
DN 120:235834
TI 3-Hydroxy-3-methyl glutaryl coenzyme A reductase inhibition modulates vasopressin-stimulated Ca2+ responses in rat A10 vascular

smooth muscle cells
AU Ng, Leong L.; Davies, Joan E.; Wojcikiewicz, Richard J. H.
CS Dep. Pharmacol., Leicester R. Infirmary, Leicester, LE2 7LX, UK
SO Circ. Res. (1994), 74(2), 173-81
CODEN: CIRUAL; ISSN: 0009-7330
DT Journal
LA English
AB Previous evidence has indicated a role for changes in cell membrane cholesterol in the modulation of [Ca2+]i responses and smooth muscle contraction to vascular agonists. However, the actions of plasma cholesterol-lowering agents such as 3-hydroxy-3-Me glutaryl CoA reductase inhibitors (eg, simvastatin) have not been defined. Such agents may in addn. affect isoprenoid intermediates that may play a role in signal transduction pathways involving G proteins. Arginine vasopressin-induced [Ca2+]i responses in A10 rat vascular myocytes were therefore studied in vitro. Vasopressin stimulated an initial peak [Ca2+]i that was independent of extracellular Ca2+ entry and a subsequent plateau that was dependent on Ca2+ influx, mainly through receptor-operated dihydropyridine-insensitive divalent cation channels. Simvastatin-treated A10 cells (5 mg/L for 24 h) showed a normal initial peak response to vasopressin, but the plateau phase of Ca2+ entry was significantly impaired. By use of Mn2+ quenching of intracellular fura 2 to measure divalent cation entry, the maximal rate of vasopressin-stimulated Mn2+ entry was impaired in simvastatin-treated cells by 52%. Mevalonate (1 mmol/L for 4 h at 37.degree.) reversed all the changes in simvastatin-treated cells. There were no assocd. changes in total cellular cholesterol or fluorescence anisotropy measurements with simvastatin treatment. Measurements of inositol-1,4,5-trisphosphate mass showed that simvastatin did not impair the initial peak response to vasopressin but significantly reduced the subsequent plateau phase. These changes were also reversed with mevalonate incubation. These findings suggest that simvastatin has addnl. effects on [Ca2+]i homeostasis that are independent of changes in total cell cholesterol.
IT **9028-35-7**, 3-Hydroxy-3-methyl glutaryl coenzyme A reductase
RL: BIOL (Biological study)
(inhibitor of, simvastatin as, calcium metab. by vascular smooth muscle cells response to vasopressin in relation to)
CC 1-10 (Pharmacology)
Section cross-reference(s): 2
IT 113-79-1, **Arginine** vasopressin
RL: BIOL (Biological study)
(calcium vascular smooth muscle cells response to, hydroxymethyl glutaryl CoA reductase inhibitor simvastatin effect on, mechanism of)
IT **9028-35-7**, 3-Hydroxy-3-methyl glutaryl coenzyme A reductase
RL: BIOL (Biological study)
(inhibitor of, simvastatin as, calcium metab. by vascular smooth muscle cells response to vasopressin in relation to)

L19 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 1997 ACS
AN 1987:31721 HCAPLUS
DN 106:31721
TI Lysine:**arginine** ratio of protein and its effect on cholesterol metabolism
AU Rajamohan, T.; Kurup, P. A.
CS Dep. Biochem., Univ. Kerala, Trivandrum, 695 581, India
SO Indian J. Biochem. Biophys. (1986), 23(5), 294-6

CODEN: IJBBBQ; ISSN: 0301-1208
DT Journal
LA English
AB The lysine [56-87-1]:arginine [**74-79-3**] ratio of dietary protein had significant effect on the metab. of cholesterol [57-88-5] in rats fed a cholesterol-high diet. A Lys:Arg ratio of 1.0 significantly lowered cholesterol in the serum, liver, and aorta and increased hepatic cholesterogenesis as well as degrdn. of cholesterol to bile acids when compared to a Lys:Arg ratio of 2.0. Activity of lipoprotein lipase [9004-02-8] in the extrahepatic tissues and that of plasma lecithin cholesterol acyltransferase [9031-14-5] were also higher with a Lys:Arg ratio of 1.0. A Lys:Arg ratio of the protein of 0.5 led to hypocholesterolemia values in between those obsd. at Lys:Arg ratios of 1.0 and 2.0.
IT **74-79-3**, **Arginine**, biological studies
RL: BIOL (Biological study)
(cholesterol metab. response to lysine ratio to, of dietary proteins)
IT **9028-35-7**, Hydroxymethylglutaryl-CoA reductase
RL: BIOL (Biological study)
(lysine to **arginine** ratio of dietary proteins effect on)
CC 18-3 (Animal Nutrition)
Section cross-reference(s): 13
ST lysine **arginine** ratio diet cholesterol metab; protein lysine **arginine** diet cholesterol metab
IT Heart, composition
Kidney, composition
Liver, composition
(cholesterol of, lysine to **arginine** ratio in dietary proteins effect on)
IT Bile acids
RL: FORM (Formation, nonpreparative)
(formation of, from cholesterol, lysine to **arginine** ratio of dietary proteins effect on)
IT Adipose tissue, composition
(lipoprotein lipase of, lysine to **arginine** ratio of dietary proteins effect on)
IT Proteins, biological studies
RL: BIOL (Biological study)
(lysine to **arginine** ratio of dietary, cholesterol metab. response to)
IT Artery, composition
(aorta, cholesterol of, lysine to **arginine** ratio in dietary proteins effect on)
IT 56-87-1, Lysine, biological studies
RL: BIOL (Biological study)
(cholesterol metab. response to **arginine** ratio to, of dietary proteins)
IT **74-79-3**, **Arginine**, biological studies
RL: BIOL (Biological study)
(cholesterol metab. response to lysine ratio to, of dietary proteins)
IT 9004-02-8, Lipoprotein lipase **9028-35-7**, Hydroxymethylglutaryl-CoA reductase
RL: BIOL (Biological study)
(lysine to **arginine** ratio of dietary proteins effect on)
IT 57-88-5, Cholesterol, biological studies

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metab. of, lysine to **arginine** ratio in dietary proteins effect on)
IT 9031-14-5, Lecithin cholesterol acyltransferase
RL: BIOL (Biological study)
(of blood plasma, lysine to **arginine** ratio of dietary proteins effect on)

L19 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 1997 ACS
AN 1982:580777 HCAPLUS
DN 97:180777
TI Effects of dietary protein on lipid metabolism in rats
AU Kritchevsky, David; Tepper, Shirley A.; Czarnecki, Susanne K.; Mueller, Maryann A.; Klurfeld, David M.
CS Wistar Inst. Anat. Biol., Philadelphia, PA, 19104, USA
SO Symp. Giovanni Lorenzini Found. (1982), 13(Lipoproteins Coron. Atheroscler.), 257-64
CODEN: SGLFD9; ISSN: 0166-1167
DT Journal
LA English
AB The effect of various animal and vegetable proteins on exptl. atherosclerosis and cholesterol [57-88-5] and lipid metab. was studied in several series of tests on rats. In the 1st series, rats given diets contg. 25% casein, soybean, casein + arginine [**74-79-3**], or soybean + lysine [56-87-1] showed blood serum cholesterol levels of 71, 64, 57, and 62 mg/dL, resp. In the 2nd series in which various levels of beef and textured vegetable proteins were compared, the lowest (43 mg/dL) cholesterol level was obsd. on the 100% vegetable protein diet, and the highest (75 mg/dL) on the diet contg. a 50:50 mixt. of these proteins. In the 3rd series, diets contg. 25% casein or 14% tallow were more cholesterogenic than a diet of 25% beef protein. In the 4th series, in which the effects of 25% casein, fish protein, whole milk protein, and beef protein diets were compared, the fish protein caused the lowest (37 vs. 53-54 mg/dL) cholesterol level. Data on the effect of various protein-contg. diets on the blood serum and liver triglycerides, phospholipids, and proteins are given. The activity of hepatic cholesterol 7.alpha.-hydroxylase [39346-35-5] and hydroxymethylglutaryl-CoA reductase [**9028-35-7**] were markedly affected by the type and level of protein and amino acids added.
IT **74-79-3**, biological studies
RL: BIOL (Biological study)
(blood cholesterol and lipids response to dietary proteins and)
IT **9028-35-7**
RL: BIOL (Biological study)
(of liver, dietary proteins effect on, cholesterol and lipids of blood serum in relation to)
CC 18-3 (Animal Nutrition)
IT 56-87-1, biological studies **74-79-3**, biological studies
RL: BIOL (Biological study)
(blood cholesterol and lipids response to dietary proteins and)
IT **9028-35-7** 39346-35-5
RL: BIOL (Biological study)
(of liver, dietary proteins effect on, cholesterol and lipids of blood serum in relation to)

L35 ANSWER 1 OF 13 HCAPLUS COPYRIGHT 1997 ACS
AN 1997:456086 HCAPLUS
DN 127:145194
TI Combined use of angiotensin inhibitors and nitric oxide stimulators to **treat** fibrosis
IN Chobanian, Aram; Brecher, Peter
PA Trustees of Boston University, USA
SO U.S., 5 pp.
CODEN: USXXAM
PI US 5645839 A 970708
AI US 95-482819 950607
DT Patent
LA English
AB A combination of angiotensin inhibitors and nitric oxide stimulators is used to slow and reverse the process of fibrosis in the body. This combination of medicaments is particularly useful in the treatment of a variety of cardiovascular fibrotic pathologies, such as that assocd. with left ventricular hypertrophy secondary to hypertension, myocardial infarction, and myocarditis.
IT **74-79-3**, L-**Arginine**, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(angiotensin inhibitor-nitric oxide stimulator combination for fibrosis **treatment**)
IT **125978-95-2**, **Nitric oxide synthase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(stimulators; angiotensin inhibitor-nitric oxide stimulator combination for fibrosis **treatment**)
IC ICM A61K009-00
NCL 424400000
CC 1-12 (Pharmacology)
IT Angiotensin II receptor antagonists
Angiotensin-converting enzyme inhibitors
Antianginal agents
Antiarrhythmic drugs
Anticoagulants
Antihypertensives
Antihypotensives
Calcium channel blockers
Diuretics
Fibrosis
Hypolipemic agents
Keloid
Potassium channel openers
Pulmonary fibrosis
Thrombolytics
Vasodilators
.alpha.-Adrenoceptor antagonists
.beta.-Adrenoceptor antagonists
(angiotensin inhibitor-nitric oxide stimulator combination for fibrosis **treatment**)
IT Cardiac glycosides
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(angiotensin inhibitor-nitric oxide stimulator combination for fibrosis **treatment**)
IT **Cardiovascular agents**
(cardioplegic; angiotensin inhibitor-nitric oxide stimulator

combination for fibrosis **treatment**)
IT Adult respiratory distress syndrome
Arteriosclerosis
Cirrhosis (liver)
Inflammation
Myocardial infarction
Myocarditis
Scleroderma
(fibrosis assocd. with; angiotensin inhibitor-nitric oxide stimulator combination for fibrosis **treatment**)
IT Cardiovascular diseases
(fibrosis; angiotensin inhibitor-nitric oxide stimulator combination for fibrosis **treatment**)
IT Skin diseases
(hypertrophic scar; angiotensin inhibitor-nitric oxide stimulator combination for fibrosis **treatment**)
IT Hypertension
(left ventricular hypertrophy secondary to, fibrosis assocd. with; angiotensin inhibitor-nitric oxide stimulator combination for fibrosis **treatment**)
IT Fibronectins
Type III collagen
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(mRNA; angiotensin inhibitor-nitric oxide stimulator combination for fibrosis **treatment**)
IT Resins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(potassium-removing; angiotensin inhibitor-nitric oxide stimulator combination for fibrosis **treatment**)
IT Left ventricular hypertrophy
(secondary to hypertension, fibrosis assocd. with; angiotensin inhibitor-nitric oxide stimulator combination for fibrosis **treatment**)
IT **74-79-3**, L-**Arginine**, biological studies
50903-99-6, L-NAME
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(angiotensin inhibitor-nitric oxide stimulator combination for fibrosis **treatment**)
IT 114798-26-4, Losartan
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(angiotensin inhibitor-nitric oxide stimulator combination for fibrosis **treatment**)
IT 55-63-0, Nitroglycerin 78-11-5, Pentaerythritol tetranitrate 87-33-2, Isosorbide dinitrate 139-33-3, Disodium edetate 1002-16-0, Amyl nitrate 15078-28-1, Nitroprusside 62571-86-2, Captopril 74258-86-9, Alacepril 75847-73-3, Enalapril 76420-72-9, Enalaprilat 76547-98-3, Lisinopril 80830-42-8, Rentiapril 81872-10-8, Zofenopril 82834-16-0, Perindopril 82924-03-6, Pentopril 83435-66-9, Delapril 83647-97-6, Spirapril 85441-61-8, Quinapril 87333-19-5, Ramipril 88768-40-5, Cilazapril 98048-97-6, Fosinopril 111223-26-8, Ceranapril
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(angiotensin inhibitor-nitric oxide stimulator combination for fibrosis **treatment**)
IT 11128-99-7, Angiotensin II
RL: BPR (Biological process); BSU (Biological study, unclassified);

BIOL (Biological study); PROC (Process)
(antagonists and catabolism activators; angiotensin inhibitor-nitric oxide stimulator combination for fibrosis **treatment**)

IT 7440-09-7, Potassium, biological studies
RL: BSU (Biological study, unclassified); REM (Removal or disposal); BIOL (Biological study); PROC (Process)
(channel, activators, and potassium-removing resins; angiotensin inhibitor-nitric oxide stimulator combination for fibrosis **treatment**)

IT 7440-70-2, Calcium, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(channel, blockers; angiotensin inhibitor-nitric oxide stimulator combination for fibrosis **treatment**)

IT 1407-47-2, Angiotensin
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(inhibitors; angiotensin inhibitor-nitric oxide stimulator combination for fibrosis **treatment**)

IT 9015-82-1, Angiotensin-converting enzyme 9025-82-5, Phosphodiesterase 9041-90-1, Angiotensin I
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; angiotensin inhibitor-nitric oxide stimulator combination for fibrosis **treatment**)

IT 85637-73-6, Atrial natriuretic factor
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(mRNA; angiotensin inhibitor-nitric oxide stimulator combination for fibrosis **treatment**)

IT 10102-43-9, Nitric oxide, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(stimulators; angiotensin inhibitor-nitric oxide stimulator combination for fibrosis **treatment**)

IT **125978-95-2, Nitric oxide synthase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(stimulators; angiotensin inhibitor-nitric oxide stimulator combination for fibrosis **treatment**)

L35 ANSWER 2 OF 13 HCAPLUS COPYRIGHT 1997 ACS
AN 1997:72319 HCAPLUS
DN 126:84614
TI Methods using nitric oxide scavengers for in vivo reduction of nitric oxide levels, compositions, and methods for disease **treatment**
IN Lai, Ching-San
PA Mcw Research Foundation, Inc., USA; Lai, Ching-San
SO PCT Int. Appl., 52 pp.
CODEN: PIXXD2
PI WO 9638457 A1 961205
DS W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, NL, PT, SE
AI WO 96-US2605 960227
PRAI US 95-459518 950602

US 95-554196 951106
DT Patent
LA English
OS MARPAT 126:84614

AB Methods are provided for the in vivo redn. of nitric oxide levels in a mammalian subject. In contrast to the inhibitory approach described in the prior art (i.e., wherein the function of the enzymes responsible for nitric oxide prodn. is inhibited), the present invention employs a scavenging approach whereby overproduced nitric oxide is bound in vivo to a suitable nitric oxide scavenger. The resulting complex renders the nitric oxide harmless, and is eventually excreted in the urine of the host. Further in accordance with the present invention, there are provided compns. and formulations useful for carrying out the above-described methods. Furthermore, the present invention relates to methods for reducing in vivo levels of NO as a means of treating subjects afflicted with inflammatory and/or infectious disease. Dithiocarbamate-contg. nitric oxide scavengers are administered to a host in need of such treatment; these scavengers interact with in vivo produced NO, forming stable dithiocarbamate-metal-NO complex. The NO-contg. complex is then filtered through the kidneys, concd. in the urine, and eventually excreted by the subject, thereby reducing in vivo NO levels.

IT **125978-95-2, Nitric oxide synthase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(nitric oxide scavengers for in vivo redn. of nitric oxide levels, compns., and methods for disease **treatment**)
IC ICM C07F013-00
ICS C07F001-08; C07F015-02; C07F015-06
CC 1-12 (Pharmacology)
Section cross-reference(s): 63
ST nitric oxide scavenger pharmaceutical **therapeutic**
IT Extracorporeal circulation
(cardiopulmonary bypass, nitric oxide overprodn. assocd. with; nitric oxide scavengers for in vivo redn. of nitric oxide levels, compns., and methods for disease **treatment**)
IT Ileum
(disease, ileitis, nitric oxide overprodn. assocd. with; nitric oxide scavengers for in vivo redn. of nitric oxide levels, compns., and methods for disease **treatment**)
IT Liquid dosage forms (drug delivery systems)
(dispersions; nitric oxide scavengers for in vivo redn. of nitric oxide levels, compns., and methods for disease **treatment**)
IT Drug delivery systems
(enteric-coated; nitric oxide scavengers for in vivo redn. of nitric oxide levels, compns., and methods for disease **treatment**)
IT Inflammatory bowel diseases
(ileitis, nitric oxide overprodn. assocd. with; nitric oxide scavengers for in vivo redn. of nitric oxide levels, compns., and methods for disease **treatment**)
IT Inflammation
(liver or **kidney**, nitric oxide overprodn. assocd. with; nitric oxide scavengers for in vivo redn. of nitric oxide levels, compns., and methods for **disease treatment**)
IT Meningitis
(lymphocytic chorio-, nitric oxide overprodn. assocd. with;

nitric oxide scavengers for in vivo redn. of nitric oxide levels, compns., and methods for disease **treatment**)

IT Drug delivery systems
(micelles; nitric oxide scavengers for in vivo redn. of nitric oxide levels, compns., and methods for disease **treatment**)

IT Cytokines
Interferon .gamma.
Interleukin 1
Interleukin 12
Interleukin 2
Interleukin 6
Tumor necrosis factors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(nitric oxide overprodn. assocd. with administration of; nitric oxide scavengers for in vivo redn. of nitric oxide levels, compns., and methods for disease **treatment**)

IT **Kidney**
Liver
(nitric oxide overprodn. assocd. with inflammation of; nitric oxide scavengers for in vivo redn. of nitric oxide levels, compns., and methods for **disease treatment**)

IT Alzheimer's disease
Anaphylaxis
Arthritis
Asthma
Burn
Chronic fatigue syndrome
Cirrhosis (liver)
Crohn's disease
Diabetes mellitus
Encephalomyelitis
Glomerulonephritis
Hemodialysis
Hemorrhagic shock
Infection
Ischemia
Meningitis
Multiple sclerosis
Pancreatitis
Parkinson's disease
Peritonitis
Reperfusion injury
Septic shock
Stroke
Tumors (animal)
Ulcer
Ulcerative colitis
Uveitis
Vasculitis
(nitric oxide overprodn. assocd. with; nitric oxide scavengers for in vivo redn. of nitric oxide levels, compns., and methods for disease **treatment**)

IT Antibiotics
Cardiovascular agents
(nitric oxide scavengers for in vivo redn. of nitric oxide levels, compns., and methods and combinations with other agents for disease **treatment**)

IT Catecholamines, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide scavengers for in vivo redn. of nitric oxide levels, compns., and methods and combinations with other agents for disease **treatment**)
IT Antihypotensives
Emulsions (drug delivery systems)
Inhalants (drug delivery systems)
Intravenous injections
Liposomes (drug delivery systems)
Oral drug delivery systems
Parenteral solutions (drug delivery systems)
Scavengers
Solid dosage forms (drug delivery systems)
Solutions (drug delivery systems)
Subcutaneous injections
(nitric oxide scavengers for in vivo redn. of nitric oxide levels, compns., and methods for disease **treatment**)
IT Drug delivery systems
(rectal; nitric oxide scavengers for in vivo redn. of nitric oxide levels, compns., and methods for disease **treatment**)
IT Allotransplant
(rejection, nitric oxide overprodn. assocd. with; nitric oxide scavengers for in vivo redn. of nitric oxide levels, compns., and methods for disease **treatment**)
IT Transition metal complexes
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(with dithiocarbamates; nitric oxide scavengers for in vivo redn. of nitric oxide levels, compns., and methods for disease **treatment**)
IT 51-41-2, Noradrenaline 51-61-6, Dopamine, biological studies 34368-04-2, Dobutamine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide scavengers for in vivo redn. of nitric oxide levels, compns., and methods and combinations with other agents for disease **treatment**)
IT 10102-43-9, Nitric oxide, biological studies
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(nitric oxide scavengers for in vivo redn. of nitric oxide levels, compns., and methods for disease **treatment**)
IT 17035-90-4, NG-Monomethyl-L-**arginine**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(nitric oxide scavengers for in vivo redn. of nitric oxide levels, compns., and methods for disease **treatment**)
IT 94161-07-6D, N-Methyl-D-glucamine dithiocarbamate, iron complexes
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide scavengers for in vivo redn. of nitric oxide levels, compns., and methods for disease **treatment**)
IT 14797-55-8, Nitrate, biological studies 14797-65-0, Nitrite, biological studies
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(nitric oxide scavengers for in vivo redn. of nitric oxide levels, compns., and methods for disease **treatment**)
IT **125978-95-2, Nitric oxide**

synthase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(nitric oxide scavengers for in vivo redn. of nitric oxide levels, compns., and methods for disease **treatment**)

IT 594-07-0D, Dithiocarbamic acid, derivs., complexes 7439-89-6D, Iron, dithiocarbamate complexes 7439-96-5D, Manganese, dithiocarbamate complexes 7440-48-4D, Cobalt, dithiocarbamate complexes 7440-50-8D, Copper, dithiocarbamate complexes
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide scavengers for in vivo redn. of nitric oxide levels, compns., and methods for disease **treatment**)

L35 ANSWER 3 OF 13 HCAPLUS COPYRIGHT 1997 ACS
AN 1997:26304 HCAPLUS
DN 126:42700
TI Endothelin antagonists and endothelin synthase inhibitors for the prevention and **treatment** of uterine contractility disorders, preeclampsia, atherosclerotic vascular disease, hypertension and for hormone replacement **therapy**
IN Chwakisz, Kristof; Garfield, Robert E.
PA Chwakisz, Kristof, Germany; Garfield, Robert, E.
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
PI WO 9635453 A2 961114
DS W: AL, AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, UG, UZ, VN
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 95-US15220 951130
PRAI US 95-437462 950508
DT Patent
LA English
AB A pharmaceutical compn. for and methods of treatment of menstrual disorders, e.g., dysmenorrhea, in a non-pregnant female, preterm labor, preeclampsia and/or fetal growth retardation in a pregnant female mammal, treatment of atherosclerotic vascular disease and hypertension in males as well as females, and for hormone replacement therapy in peri- and post-menopausal females, comprising administering effective amts. of an endothelin antagonist and/or an endothelin synthase inhibitor or both, in combination with (a) a progestin, and/or and estrogen, and/or (b) a cyclooxygenase inhibitor, and/or (c) a nitric oxide substrate, to prevent and/or ameliorate said conditions, are disclosed. In the method aspects, the endothelin antagonist and/or endothelin synthase inhibitor can be administered alone fro treatment of menstrual disorders, e.g., dysmenorrhea, in a non-pregnant female, preterm labor, preeclampsia and/or feta growth retardation in a pregnant female mammal. Further, methods for screening compds. such treatments are disclosed.
IT **74-79-3**, L-**Arginine**, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin antagonists and endothelin synthase inhibitors for the prevention and **treatment** of uterine diseases and menstrual disorders)
IT **125978-95-2**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; endothelin antagonists and endothelin synthase

inhibitors for the prevention and **treatment** of uterine diseases and menstrual disorders)

IC ICM A61K045-06
ICS A61K038-12; A61K031-57; A61K031-60; A61K031-565; A61K031-42; A61K031-22

CC 1-10 (Pharmacology)
Section cross-reference(s): 2

IT Antiatherosclerotics
Antihypertensives
Dysmenorrhea
Menstrual disorders
Preeclampsia
Preterm labor
Uterine diseases
(endothelin antagonists and endothelin synthase inhibitors for the prevention and **treatment** of uterine diseases and menstrual disorders)

IT Estrogens
Progestins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin antagonists and endothelin synthase inhibitors for the prevention and **treatment** of uterine diseases and menstrual disorders)

IT Fetus
(intrauterine growth retardation; endothelin antagonists and endothelin synthase inhibitors for the prevention and **treatment** of uterine diseases and menstrual disorders)

IT 116243-73-3, Endothelin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antagonists; endothelin antagonists and endothelin synthase inhibitors for the prevention and **treatment** of uterine diseases and menstrual disorders)

IT 10102-43-9, Nitric oxide, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(donors and substrates; endothelin antagonists and endothelin synthase inhibitors for the prevention and **treatment** of uterine diseases and menstrual disorders)

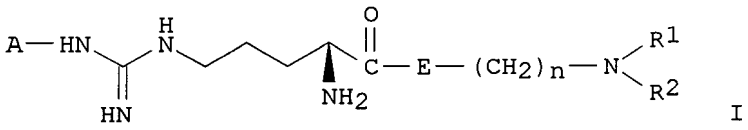
IT 136553-81-6, BQ-123 153042-42-3, BMS182874 185036-49-1, SQ 28608
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin antagonists and endothelin synthase inhibitors for the prevention and **treatment** of uterine diseases and menstrual disorders)

IT 50-78-2, Aspirin 57-83-0, Progesterone, biological studies
74-79-3, L-**Arginine**, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin antagonists and endothelin synthase inhibitors for the prevention and **treatment** of uterine diseases and menstrual disorders)

IT 39391-18-9, Cyclooxygenase **125978-95-2**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; endothelin antagonists and endothelin synthase inhibitors for the prevention and **treatment** of uterine diseases and menstrual disorders)

L35 ANSWER 4 OF 13 HCAPLUS COPYRIGHT 1997 ACS
AN 1996:646511 HCAPLUS
DN 125:276575

TI Preparation of **arginine** analogs having **nitric oxide synthase** inhibitor activity
IN Broquet, Colette; Chabrier, De Lassauniere, Pierre-Etienne
PA Societe De Conseils De Recherches Et D'application, Fr.
SO PCT Int. Appl., 32 pp.
CODEN: PIXXD2
PI WO 9627593 A1 960912
DS W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, NL, PT, SE
AI WO 96-FR337 960304
PRAI GB 95-4350 950304
DT Patent
LA French
OS MARPAT 125:276575
GI



I

AB L-Arginine derivs. [I; A = H, lower alkyl, NO2; E = O, bond; R1, R2 = (un)branched alkyl; n = 0-12; NR1R2 = heterocyclyl], useful as nitric oxide synthase inhibitors for the treatment of cardiovascular, bronchopulmonary, gastrointestinal, genitourinary, or CNS disorders, are prepd. Thus, I (A = NO2; E = O; n = 6; NR1R2 = 1-morpholinyl) dihydrochloride was prepd. (from 6-morpholinohexanol) and demonstrated a nitric oxide synthase IC50 of 5 .mu.M, vs. >100 .mu.M for aminoguanidine.
IT **125978-95-2, Nitric oxide synthase**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(prepn. of **arginine** analogs having **nitric oxide synthase** inhibitor activity)
IC ICM C07D295-088
ICS C07C279-36; C07D521-00; C07C279-14; A61K031-155; A61K031-435; A61K031-535; A61K031-415
CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1
ST **arginine** prepn **nitric oxide synthase** inhibitor; **cardiovascular agent nitric oxide synthase** inhibitor; CNS agent **nitric oxide synthase** inhibitor; bronchodilator prepn **nitric oxide synthase** inhibitor
IT Nervous system agents
(**arginine** analogs)
IT Bronchodilators
Cardiovascular agents
Inflammation inhibitors

(**arginine** analogs having **nitric oxide** **synthase** inhibitor activity)

IT Digestive tract
(disease, **arginine** analogs having **nitric** **oxide synthase** inhibitor activity for **treatment** of)

IT 182576-02-9P
RL: BAC (Biological activity or effector, except adverse); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of **arginine** analogs having **nitric** **oxide synthase** inhibitor activity)

IT 182575-92-4P 182575-93-5P 182575-94-6P 182575-95-7P
182575-96-8P 182575-97-9P 182575-98-0P 182575-99-1P
182576-00-7P 182576-01-8P 182576-04-1P 182576-05-2P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of **arginine** analogs having **nitric** **oxide synthase** inhibitor activity)

IT **125978-95-2, Nitric oxide** **synthase**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(prepn. of **arginine** analogs having **nitric** **oxide synthase** inhibitor activity)

IT 50-78-2, Acetylsalicylic acid 110-91-8, Morpholine, reactions
622-40-2, 4-Morpholineethanol 1615-14-1, 1H-Imidazole-1-ethanol
2188-18-3 2304-98-5 3040-44-6, 1-Piperidineethanol 4441-30-9,
4-Morpholinepropanol 15687-27-1, Ibuprofen 17719-81-2,
6-Morpholino-1-hexanol
RL: RCT (Reactant)
(prepn. of **arginine** analogs having **nitric** **oxide synthase** inhibitor activity)

IT 182576-06-3P 182576-07-4P 182576-08-5P 182576-09-6P
182576-10-9P 182576-11-0P 182576-12-1P 182576-13-2P
182576-14-3P 182576-15-4P 182576-16-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of **arginine** analogs having **nitric** **oxide synthase** inhibitor activity)

L35 ANSWER 5 OF 13 HCAPLUS COPYRIGHT 1997 ACS
AN 1996:428485 HCAPLUS
DN 125:76383
TI Method and formulation of stimulating nitric oxide synthesis using **therapeutic** mixture of L-**arginine** and nitroglycerin, and use for **treatment** of diseases related to vasoconstriction
IN Kaesemeyer, W. H.
PA USA
SO PCT Int. Appl., 39 pp.
CODEN: PIXXD2
PI WO 9610910 A1 960418
DS W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG

AI WO 95-US12780 951005
PRAI US 94-321051 941005
DT Patent
LA English
AB A therapeutic mixt. comprising a mixt. of L-arginine and an agonist of nitric oxide synthase, namely nitroglycerin, is disclosed for the treatment of diseases related to vasoconstriction, wherein the vasoconstriction is relieved by stimulating the constitutive form of nitric oxide synthase (cNOS) to produce native nitric oxide (NO), the native NO having superior beneficial effect when compared to exogenous NO produced by an L-arginine independent pathway in terms of the ability to reduce clin. endpoints and mortality. The formation of a complex or coordinate between L-arginine and nitroglycerin, when the two are mixed, is described, as are results from animal and human studies. In a study with a normal human volunteer, results indicated that administration of combined L-arginine-nitroglycerin does not have the adverse consequences seen with either L-arginine or nitroglycerin when administered alone.
IT **74-79-3**, L-**Arginine**, biological studies
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide synthesis stimulation using **therapeutic** mixt. of L-**arginine** and nitroglycerin, and use for **treatment** of diseases related to vasoconstriction)
IT **125978-95-2**, **Nitric oxide synthase**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(nitric oxide synthesis stimulation using **therapeutic** mixt. of L-**arginine** and nitroglycerin, and use for **treatment** of diseases related to vasoconstriction)
IT **74-79-3D**, L-**Arginine**, complexes with nitroglycerin
RL: FMU (Formation, unclassified); FORM (Formation, nonpreparative)
(nitric oxide synthesis stimulation using **therapeutic** mixt. of L-**arginine** and nitroglycerin, and use for **treatment** of diseases related to vasoconstriction)
IC ICM A01N037-12
CC 1-8 (Pharmacology)
ST **vasodilator** combination **arginine** nitroglycerin; cardiovascular disease **treatment arginine** nitroglycerin
IT **Antihypertensives**
Cardiovascular agents
Vasodilators
(nitric oxide synthesis stimulation using **therapeutic** mixt. of L-**arginine** and nitroglycerin, and use for **treatment** of diseases related to vasoconstriction)
IT **Brain, disease**
(cerebrovascular, nitric oxide synthesis stimulation using **therapeutic** mixt. of L-**arginine** and nitroglycerin, and use for **treatment** of **diseases** related to vasoconstriction)
IT **Heart, disease**
(coronary, nitric oxide synthesis stimulation using **therapeutic** mixt. of L-**arginine** and nitroglycerin, and use for **treatment** of **diseases** related to vasoconstriction)
IT Cardiovascular system

(disease, nitric oxide synthesis stimulation using **therapeutic** mixt. of L-**arginine** and nitroglycerin, and use for **treatment** of diseases related to vasoconstriction)

IT **Kidney, disease**
(ischemia, nitric oxide synthesis stimulation using **therapeutic** mixt. of L-**arginine** and nitroglycerin, and use for **treatment** of **diseases** related to vasoconstriction)

IT 55-63-0, Nitroglycerin **74-79-3**, L-**Arginine**, biological studies
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide synthesis stimulation using **therapeutic** mixt. of L-**arginine** and nitroglycerin, and use for **treatment** of diseases related to vasoconstriction)

IT **125978-95-2, Nitric oxide synthase**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(nitric oxide synthesis stimulation using **therapeutic** mixt. of L-**arginine** and nitroglycerin, and use for **treatment** of diseases related to vasoconstriction)

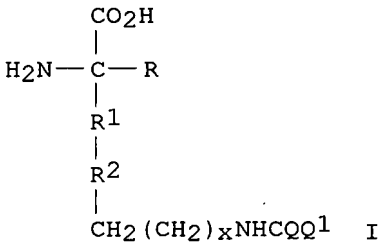
IT 10102-43-9, Nitric oxide, biological studies
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(nitric oxide synthesis stimulation using **therapeutic** mixt. of L-**arginine** and nitroglycerin, and use for **treatment** of diseases related to vasoconstriction)

IT 55-63-0D, Nitroglycerin, complexes with L-**arginine** **74-79-3D**, L-**Arginine**, complexes with nitroglycerin
RL: FMU (Formation, unclassified); FORM (Formation, nonpreparative)
(nitric oxide synthesis stimulation using **therapeutic** mixt. of L-**arginine** and nitroglycerin, and use for **treatment** of diseases related to vasoconstriction)

IT 50-56-6, Oxytocin, biological studies 51-45-6, Histamine, biological studies 51-84-3, Acetylcholine, biological studies 52-90-4, Cysteine, biological studies 56-65-5, Adenosine triphosphate, biological studies 58-82-2, Bradykinin 70-49-5 110-46-3, Isoamyl nitrite 551-11-1 616-91-1, N-Acetylcysteine 3483-12-3, Dithiothreitol 3724-10-5 7697-37-2D, Nitric acid, esters 11000-17-2, Vasopressin 14402-89-2, Sodium nitroprusside 33507-63-0, Substance P 33876-97-0, SIN-1 52665-69-7, A23187 178626-82-9
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide synthesis stimulation using **therapeutic** mixt. of L-**arginine** and nitroglycerin, and use for **treatment** of diseases related to vasoconstriction)

L35 ANSWER 6 OF 13 HCAPLUS COPYRIGHT 1997 ACS
AN 1995:606655 HCAPLUS
DN 123:9923
TI Preparation of heme binding amino acid derivatives as inhibitors of nitric oxide formation from **arginine**
IN Griffith, Owen W.; Narayanan, Krishnaswamy
PA Medical College of Wisconsin Research Foundation, Inc., USA
SO PCT Int. Appl., 52 pp.
CODEN: PIXXD2

PI WO 9501972 A1 950119
DS W: CA, JP
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AI WO 94-US4554 940506
PRAI US 93-87371 930707
DT Patent
LA English
OS MARPAT 123:9923
GI



I

AB Physiol. active amino acid compds. including N.delta.-substituted ornithine or N.epsilon.-substituted lysine moieties or monoalkyl carbon-substituted N.delta.-substituted ornithine or N.epsilon.-substituted lysine moieties, having formula [I; R = (CH2)yMe or H; R1, R2 = CH2, CH[(CH2)yMe]; y = 0 to 5; x = 0 or 1; wherein none or only one of R, R1 and R2 provides an alkyl substituent on ornithine or lysine moiety; Q = a heme binding moiety and/or a sulfur-contg. binding moiety; Q1 = NH2 when there is a double bond between the omega carbon and Q and Q1 = NH when there is a single bond between the omega carbon and Q] and physiol. acceptable acid addn. salts thereof are prepd. These amino acid derivs. I are useful for treating hypotension, inflammation, and stroke and to restore vascular contractile sensitivity to the effects of adrenergic agonists. Thus, 5.80 g Boc-Orn-OCMe3 was dissolved in CHCl3 and added to a soln. of 5.70 g CaCO3 and 2.2 mL SOCl2 in 100 mL H2O followed by vigorously stirring the mixt. overnight to give an oil, Boc-Orn(SOCl)-OCMe3. The latter oil was taken up in MeOH and cooled to 0.degree. and to the resulting soln. was passed NH3(g) for 20 min to give L-H2NC(S)NH(CH2)3CH(NHBoc)CO2CMe3 which was treated with a soln. of 4N HCl in dioxane at room temp. for 24 h to give N.delta.-thioureido-L-norvaline (L-thiocitrulline) (II). II at 100 .mu.M in vitro showed virtually complete inhibition of nitric oxide synthase induced by interleukin 1 and interferon-gamma in the culture of rat aortic smooth muscle cells. II at 20 mg/kg (bolus injection) in vivo blocked basal nitric oxide formation in rats and as a result effected the increase in systolic, diastolic, and mean arterial pressures.

IT **125978-95-2, Nitric oxide synthase**
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(prepn. of ornithine and lysine derivs. as **nitric oxide synthase** inhibitors)

IC ICM C07D333-22

ICS A61K031-38; C07C335-02; C07C257-14; C07C279-04; A61K031-17; A61K031-155
CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1
ST ornithine deriv prepn **antihypertensive**; lysine deriv prepn antiinflammatory; stroke **treatment** ornithine deriv; **nitric oxide synthase** inhibitor; heme binding amino acid deriv prepn
IT **Antihypertensives**
Inflammation inhibitors
(prepn. of ornithine and lysine derivs. as **nitric oxide synthase** inhibitors for **treatment** of hypertension, inflammation, and stroke)
IT **Brain, disease**
(stroke, prepn. of ornithine and lysine derivs. as **nitric oxide synthase** inhibitors for **treatment** of hypertension, inflammation, and stroke)
IT 53054-01-6P, H-Orn(Z)-OtBu 53054-02-7P, Boc-Orn(Z)-OtBu 53054-03-8P, Boc-Orn-OtBu 112157-39-8P, Z-Lys-OtBu 133565-49-8P 160203-45-2P 162049-50-5P, Methyl 2-thienylmethylimidate hydrochloride 163761-83-9P 163761-84-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(intermediate for prepn. of ornithine and lysine derivs. as **nitric oxide synthase** inhibitors)
IT 10102-43-9, Nitric oxide, biological studies
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(prepn. of heme binding amino acid (lysine and ornithine) derivs. as inhibitors of nitric oxide formation from **arginine**)
IT 156719-37-8P, L-Thiocitrulline 156719-38-9P, L-Homothiocitrulline 163761-85-1P, N.delta.-(2-Thienyl)methylimino-L-ornithine
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of ornithine and lysine derivs. as **nitric oxide synthase** inhibitors)
IT **125978-95-2, Nitric oxide synthase**
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(prepn. of ornithine and lysine derivs. as **nitric oxide synthase** inhibitors)
IT 67-56-1, Methanol, reactions 463-71-8, Thiophosgene 540-88-5, tert-Butyl acetate 2212-75-1 3184-13-2, L-Ornithine hydrochloride 3304-51-6, H-Orn(Z)-OH 7664-41-7, Ammonia, reactions 16937-91-0, H-D-Orn(Z)-OH 24424-99-5, Di-tert-Butyl pyrocarbonate 96571-18-5, Thiophenecarbonitrile
RL: RCT (Reactant)
(reaction in prepn. of ornithine and lysine derivs. as **nitric oxide synthase** inhibitors)

L35 ANSWER 7 OF 13 HCAPLUS COPYRIGHT 1997 ACS
AN 1995:403391 HCAPLUS
DN 122:151385
TI **Treatment** of stroke with nitric-oxide releasing compounds
IN Moskowitz, Michael A.
PA The General Hospital Corp., USA
SO U.S., 9 pp.
CODEN: USXXAM

PI US 5385940 A 950131
AI US 92-972267 921105
DT Patent
LA English
AB A method for treatment of stroke in a patient involves administering to the patient a nitric oxide-releasing compd. A preferred compd. of the invention is L-arginine. The effect of L-arginine in an animal stroke model is described.
IT **125978-95-2, Nitric oxide synthase**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (substrates; **treatment** of stroke with nitric-oxide releasing compds.)
IT **74-79-3**, L-**Arginine**, biological studies
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (**treatment** of stroke with nitric-oxide releasing compds.)
IC ICM A61K031-195
NCL 514565000
CC 1-8 (Pharmacology)
ST stroke **treatment** nitric oxide releasing compd; **arginine** stroke **treatment**
IT **Brain, disease** (stroke, ischemic; **treatment** of stroke with nitric-oxide releasing compds.)
IT **125978-95-2, Nitric oxide synthase**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (substrates; **treatment** of stroke with nitric-oxide releasing compds.)
IT 157-06-2, D-**Arginine**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study) (**treatment** of stroke with nitric-oxide releasing compds.)
IT **74-79-3**, L-**Arginine**, biological studies
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (**treatment** of stroke with nitric-oxide releasing compds.)
IT 10102-43-9, Nitric oxide, biological studies
RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process) (**treatment** of stroke with nitric-oxide releasing compds.)

L35 ANSWER 8 OF 13 HCAPLUS COPYRIGHT 1997 ACS
AN 1994:570586 HCAPLUS
DN 121:170586
TI Agents for targeted nitric oxide pathway or **nitric oxide synthase** modulation for **therapeutic** effect
IN Axworthy, Donald B.
PA Neorx Corp., USA
SO PCT Int. Appl., 44 pp.
CODEN: PIXXD2
PI WO 9416729 A1 940804
DS W: CA, JP

RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AI WO 94-US894 940126
PRAI US 93-10238 930128
DT Patent
LA English
AB The present invention is directed to targeted agents capable of modulating a nitric oxide pathway or nitric oxide synthase to achieve a therapeutic effect. Some preferred targeted agents include a targeting portion (e.g. an antibody or protein complementary to a target cell receptor) capable of delivering the agent to a target site and an effector portion (arginine or analogs or polymers thereof, heme, cytokines, corticosteroids, aminoguanidine, etc.) capable of modulating a nitric oxide pathway or nitric oxide synthase at the target site. The present invention also provides methods of modulating a nitric oxide pathway or nitric oxide synthase to achieve a therapeutic effect in a target cell population (e.g. vascular smooth muscle cells, corpora cavernosa smooth muscle cells, endothelial cells, brain cells, liver cells). The therapeutic objective may be treatment of restenosis, treatment of septic shock, modulation of inflammation, etc.
IT **125978-95-2**, **Nitric oxide synthase**
RL: BIOL (Biological study)
(agents with targeting portion and effector portion for modulation of, for **therapeutics**)
IT **74-79-3**, L-**Arginine**, biological studies
74-79-3D, **Arginine**, analogs **74-79-3D**, L-**Arginine**, polymers
RL: BIOL (Biological study)
(as effector portion, in agent for modulation of nitric oxide pathway or **nitric oxide synthase**)
IC ICM A61K039-395
ICS A61K031-00; A61K035-14; C07K015-28; C12N005-12
CC 1-12 (Pharmacology)
ST nitric oxide pathway modulation agent **therapeutic**; synthase nitric oxide modulation agent **therapeutic**
IT **Therapeutics**
(agents with targeting portion and effector portion for modulation of nitric oxide pathway or **nitric oxide synthase**)
IT Lymphokines and Cytokines
Corticosteroids, biological studies
RL: BIOL (Biological study)
(as effector portion, in agent for modulation of nitric oxide pathway or **nitric oxide synthase**)
IT Antibodies
Peptides, biological studies
RL: BIOL (Biological study)
(as targeting portion, in agent for modulation of nitric oxide pathway or **nitric oxide synthase**)
IT Avidins
RL: BIOL (Biological study)
(biotin-, for targeted agent for modulation of nitric oxide pathway or **nitric oxide synthase**)
IT Inflammation
(cascade function, increase of, targeted agent for modulation of nitric oxide pathway or **nitric oxide synthase** for)
IT Brain

Liver
Neoplasm
(cells of, targeted agents for modulation of nitric oxide pathway or **nitric oxide synthase** for)

IT Blood vessel
(dilation of, neurotransmitters assocd. with, as target population for hyperemia **treatment**, targeted agent for modulation of nitric oxide pathway or **nitric oxide synthase** for)

IT Receptors
RL: BIOL (Biological study)
(of target cell, protein complementary to, as targeting portion, in agent for modulation of nitric oxide pathway or **nitric oxide synthase**)

IT Radicals, biological studies
RL: BIOL (Biological study)
(oxide, scavenger for, as effector portion, in agent for modulation of nitric oxide pathway or **nitric oxide synthase**)

IT Proteins, biological studies
RL: BIOL (Biological study)
(target cell receptor-complementary, as targeting portion, in agent for modulation of nitric oxide pathway or **nitric oxide synthase**)

IT Inflammation inhibitors
(targeted agent for modulation of nitric oxide pathway or **nitric oxide synthase**)

IT Penis
(targeted agent for modulation of nitric oxide pathway or **nitric oxide synthase** for promotion of erection of)

IT Macrophage
(targeted agent for modulation of nitric oxide pathway synthesis for, for **therapy** involving proliferation or cytolytic activity of T-cells)

IT Hyperemia
(**treatment** of, targeted agent for modulation of nitric oxide pathway or **nitric oxide synthase** for)

IT Glycoproteins, specific or class
RL: BIOL (Biological study)
(40,000-mol.-wt., membrane, pancarcinoma antibody to, as targeting portion, in agent for modulation of nitric oxide pathway or **nitric oxide synthase**)

IT Lymphocyte
(T-cell, proliferation or cytolytic activity of, targeted agent for modulation of nitric oxide pathway or **nitric oxide synthase** for)

IT Penis
(corpus cavernosum, smooth muscle cells of, targeted agents for modulation of nitric oxide pathway or **nitric oxide synthase** for)

IT Nerve, disease
(degeneration, **treatment** of, targeted agent for modulation of nitric oxide pathway or **nitric oxide synthase** for)

IT Blood vessel
(endothelium, cells of, targeted agents for modulation of nitric oxide pathway or **nitric oxide**

synthase for)
IT Glycoproteins, specific or class
RL: BIOL (Biological study)
(galactose-contg., as targeting portion, in agent for modulation of nitric oxide pathway or **nitric oxide synthase**)
IT Corticosteroids, biological studies
RL: BIOL (Biological study)
(gluco-, as effector portion, in agent for modulation of nitric oxide pathway or **nitric oxide synthase**)
IT Lymphokines and Cytokines
RL: BIOL (Biological study)
(macrophage-deactivating factor, as effector portion, in agent for modulation of nitric oxide pathway or **nitric oxide synthase**)
IT Antibodies
RL: BIOL (Biological study)
(monoclonal, as targeting portion, in agent for modulation of nitric oxide pathway or **nitric oxide synthase**)
IT Neurohormones
RL: BIOL (Biological study)
(neurotransmitters, vasodilation-assocd., as target population for hyperemia **treatment**, targeted agent for modulation of nitric oxide pathway or **nitric oxide synthase** for)
IT **Heart, disease**
(restenosis, **treatment** of, targeted agent for modulation of nitric oxide pathway or **nitric oxide synthase** for)
IT Shock
(septic, **treatment** of, targeted agent for modulation of nitric oxide pathway or **nitric oxide synthase** for)
IT Muscle
(smooth, cells of, targeted agents for modulation of nitric oxide pathway or **nitric oxide synthase** for)
IT Animal growth regulators
RL: BIOL (Biological study)
(transforming growth factors, as effector portion, in agent for modulation of nitric oxide pathway or **nitric oxide synthase**)
IT 58-85-5, Biotin
RL: BIOL (Biological study)
((strept)avidin-, for targeted agent for modulation of nitric oxide pathway or **nitric oxide synthase**)
IT 55-63-0, Nitroglycerin 14402-89-2, Sodium nitroprusside 121263-19-2, Calphostin C
RL: BIOL (Biological study)
(agent for modulation of nitric oxide pathway or **nitric oxide synthase** in relation to vascular smooth muscle target cell response to)
IT **125978-95-2, Nitric oxide synthase**
RL: BIOL (Biological study)
(agents with targeting portion and effector portion for

modulation of, for **therapeutics**)
IT 56-86-0, Glutamic acid, biological studies 56-86-0D, Glutamic acid, polymers **74-79-3**, L-**Arginine**, biological studies **74-79-3D**, **Arginine**, analogs **74-79-3D**, L-**Arginine**, polymers 79-17-4, Aminoguanidine 2149-70-4 6384-92-5, N-Methyl-D-aspartic acid 6384-92-5D, N-Methyl-D-aspartic acid, polymers 14875-96-8, Heme 17035-90-4 50903-99-6 57444-72-1 139299-32-4 139299-34-6 142395-84-4
RL: BIOL (Biological study)
(as effector portion, in agent for modulation of nitric oxide pathway or **nitric oxide synthase**)
IT 9013-20-1, Streptavidin
RL: BIOL (Biological study)
(biotin-, for targeted agent for modulation of nitric oxide pathway or **nitric oxide synthase**)
IT 9068-52-4
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors, as effector portion, in agent for modulation of nitric oxide pathway or **nitric oxide synthase**)
IT 7439-89-6, Iron, biological studies
RL: BIOL (Biological study)
(non-heme, as effector portion, in agent for modulation of nitric oxide pathway or **nitric oxide synthase**)
IT 10102-43-9, Nitrogen oxide (NO), biological studies
RL: BIOL (Biological study)
(pathway, agents with targeting portion and effector portion for modulation of, for **therapeutics**)
IT 11062-77-4, Superoxide
RL: BIOL (Biological study)
(scavengers, as effector portion, in agent for modulation of nitric oxide pathway or **nitric oxide synthase**)
IT 16833-27-5D, Oxide, radicals
RL: BIOL (Biological study)
(targeted agent for modulation of nitric oxide pathway or **nitric oxide synthase** for target cell population exposed to)

L35 ANSWER 9 OF 13 HCAPLUS COPYRIGHT 1997 ACS
AN 1994:525097 HCAPLUS
DN 121:125097
TI NG-Nitro-L-**arginine** protects against ischemia-induced increases in nitric oxide and hippocampal neuro-degeneration in the gerbil
AU Caldwell, Maeve; O'Neill, Michael; Earley, Bernadette; Leonard, Brian
CS Department of Pharmacology, University College Galway, Galway, Ire.
SO Eur. J. Pharmacol. (1994), 260(2-3), 191-200
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB To assess the effects of the nitric oxide synthase inhibitor NG-Nitro-L-arginine on behavioral, biochem. and histol. changes following global ischemia, the Mongolian gerbil was used. Ischemia was induced by bilateral carotid occlusion for 5 min. NG-Nitro-L-arginine was administered i.p. at either 1 or 10 mg/kg 30

min, 6, 24, and 48 h after surgery. Five min bilateral carotid occluded animals were hyperactive 24, 48 and 72 h after surgery. NG-Nitro-L-arginine caused some attenuation in this hyperactivity. The activity of nitric oxide synthase was increased in the cerebellum, brain stem, striatum, cerebral cortex and hippocampus of 5 min bilateral carotid occluded animals. NG-Nitro-L-arginine reversed the increase in nitric oxide synthase activity in all brain regions. Extensive neuronal death was obsd. in the CA1 layer of the hippocampus in 5 min bilateral carotid occluded animals 96 h after surgery. NG-Nitro-L-arginine significantly protected against the neuronal death of cells in the CA1 layer.

IT **125978-95-2, Nitric oxide synthase**
RL: BIOL (Biological study)
(nitroarginine effect on, in brain ischemia **treatment**)

CC 1-11 (Pharmacology)
Section cross-reference(s): 14

ST nitroarginine brain ischemia nitric oxide neuroprotective; **nitric oxide synthase** brain ischemia nitroarginine; hippocampus neuroprotective nitroarginine brain ischemia

IT **Brain, disease**
(hippocampus, sector CA1, ischemia, nitroarginine neuroprotective activity in, **nitric oxide synthase** in)

IT **Brain, disease**
(ischemia, nitroarginine **treatment** of, neuroprotective activity and **nitric oxide synthase** in)

IT Cytoprotective agents
(neuroprotectants, nitroarginine as, in brain ischemia, **nitric oxide synthase** in)

IT 2149-70-4, NG-Nitro-L-**arginine**
RL: BIOL (Biological study)
(brain ischemia **treatment** with, neuroprotective activity and **nitric oxide synthase** in)

IT **125978-95-2, Nitric oxide synthase**
RL: BIOL (Biological study)
(nitroarginine effect on, in brain ischemia **treatment**)

L35 ANSWER 10 OF 13 HCAPLUS COPYRIGHT 1997 ACS
AN 1994:124656 HCAPLUS
DN 120:124656
TI A narrow **therapeutical** window of a **nitric oxide synthase** inhibitor against transient ischemic brain injury
AU Nagafuji, Toshiaki; Sugiyama, Masakazu; Matsui, Toru; Koide, Tohru
CS CNS Res. Div., Chugai Pharm. Co. Ltd., Gotenba, 412, Japan
SO Eur. J. Pharmacol., Environ. Toxicol. Pharmacol. Sect. (1993), 248(4), 325-8
CODEN: EPEPEG; ISSN: 0014-2999
DT Journal
LA English
AB N.omega.-nitro-L-arginine (0.3-10 mg/kg), a nitric oxide (NO) synthase inhibitor, was administered i.p. to gerbils subjected to 10 min of carotid artery occlusion seven times at 5 min, 3, 6, 24, 48, 72 and 96 h after recirculation. Histopathol. examn. of the brains

obtained 6 days after reflow disclosed that N.omega.-nitro-L-arginine possesses an ability to mitigate neuronal necrosis in the CA1 subfield of the hippocampus with an optimal dosage of 3 mg/kg. These results strongly suggest that NO synthase activation is at least partly involved in the pathogenetic cellular mechanisms underlying selective neuronal necrosis following cerebral ischemia.

IT **125978-95-2, Nitric oxide synthase**
RL: BIOL (Biological study)
(inhibition of, by nitroarginine, neuronal necrosis from brain ischemia and reperfusion prevention in relation to)

CC 1-11 (Pharmacology)
Section cross-reference(s): 14

ST neuron brain ischemia **nitric oxide synthase**; nitroarginine brain ischemia reperfusion nerve necrosis

IT **Brain, disease**
(cerebral cortex, ischemia, neuronal necrosis from, nitroarginine prevention of, **nitric oxide synthase** inhibition in relation to)

IT Nerve, disease
(necrosis, from cerebral ischemia and reperfusion, nitroarginine prevention of, **nitric oxide synthase** inhibition in relation to)

IT Perfusion
(re-, neuronal necrosis from cerebral ischemia and, nitroarginine prevention of, **nitric oxide synthase** inhibition in relation to)

IT **125978-95-2, Nitric oxide synthase**
RL: BIOL (Biological study)
(inhibition of, by nitroarginine, neuronal necrosis from brain ischemia and reperfusion prevention in relation to)

IT 2149-70-4, N.omega.-Nitro-L-**arginine**
RL: BIOL (Biological study)
(neuronal necrosis from brain ischemia and reperfusion prevention by, **nitric oxide synthase** inhibition in)

L35 ANSWER 11 OF 13 HCAPLUS COPYRIGHT 1997 ACS
AN 1993:581230 HCAPLUS
DN 119:181230
TI Duale inhibitors of NO synthetase und cyclooxygenase, their prepapration and pharmaceuticals containing them
IN Braquet, Pierre; Broquet, Colette; Auvin, Serge; Chabrier de Lassauniere, Piere Etienne
PA Societe de Conseils de Recherches et d'Applications Scientifiques (S.C.R.A.S.), Fr.
SO Ger. Offen., 12 pp.
CODEN: GWXXBX
PI DE 4244539 A1 930708
AI DE 92-4244539 921230
PRAI GB 92-114 920104
DT Patent
LA German
OS MARPAT 119:181230
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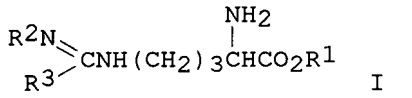

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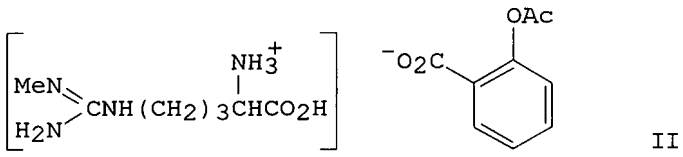

II

AB The title compds., i.e., salts AB, wherein A represents a cyclooxygenase inhibitor and B represents arginine analogs [2-amino-5-[(iminomethyl)amino]pentanoates] I (R1 = hydrogen, Me, ethyl; R2 = hydrogen, nitro; R3 = amino, methylamino, etc.) are claimed. These salts are cyclooxygenase inhibitors and nitric oxide synthetase inhibitors. Nitric oxide synthetase is an enzyme involved in guanylate cyclase-mediated transduction mechanisms in vascular system, thrombocytes, and nervous system. NO synthetase is formed as initiator in immune reactions in cells and tissue. Treatment of acetylsalicylic acid with N-methyl-L-arginine gave the aspirin .omega.-N-methylarginine salt II. I are potentially useful for the treatment of immune diseases, as cardiovascular agents, and as inflammation inhibitors (no data).

IT **125978-95-2**, Nitric oxide synthetase
RL: USES (Uses)
(inhibitors, aspirin acetylsalicylate derivs.)

IC ICM C07C279-36
ICS C07C279-14; C07C065-10; C07C069-157; C07C313-04; C07C057-30; C07C229-58; A61K031-40; A61K031-60

CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 25

ST **arginine** acetylsalicylate cyclooxygenase nitric oxide synthetase; aspirin **arginine** cyclooxygenase nitric oxide synthetase

IT **Cardiovascular agents**
Inflammation inhibitors
(aspirin acetylsalicylate derivs. (cyclooxygenase inhibitors and nitric oxide synthetase inhibitors))

IT Immunity
(disorder, **treatment** of, aspirin acetylsalicylate derivs. for (cyclooxygenase inhibitors, nitric oxide synthetase inhibitors))

IT 39391-18-9, Cyclooxygenase **125978-95-2**, Nitric oxide synthetase
RL: USES (Uses)
(inhibitors, aspirin acetylsalicylate derivs.)

IT 150022-06-3P 150022-07-4P 150022-08-5P 150269-02-6P, .omega.-N-Methyl-L-**arginine** acetylsalicylate
150269-03-7P, .omega.-N-Methyl-L-**arginine** salicylate
150269-04-8P, .omega.-N-Nitro-L-**arginine** acetylsalicylate
150269-05-9P, .omega.-N-Nitro-L-**arginine** salicylate
150269-06-0P, .omega.-N-Nitro-L-**arginine** methyl ester acetylsalicylate 150269-07-1P 150269-08-2P 150269-09-3P, Ibuprofen .omega.-N-nitro-L-**arginine** salt 150269-10-6P,

Mefenamic acid .omega.-N-nitro-L-**arginine** salt
150269-11-7P 150269-12-8P, Mefenamic acid .omega.-N-methyl-L-**arginine** salt 150269-13-9P 150269-14-0P,
.omega.-N-Nitro-L-**arginine** methyl ester salicylate
150269-15-1P 150292-03-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as cyclooxygenase inhibitor and nitric oxide synthetase inhibitor)

L35 ANSWER 12 OF 13 HCAPLUS COPYRIGHT 1997 ACS
AN 1993:551910 HCAPLUS
DN 119:151910
TI Mechanisms involved in the neuroprotective activity of a **nitric oxide synthase** inhibitor during focal cerebral ischemia
AU Buisson, A.; Margaill, I.; Callebert, J.; Plotkine, M.; Boulu, R. G.
CS Fac. Sci. Pharm. Biol., Univ. Rene Descartes, Paris, Fr.
SO J. Neurochem. (1993), 61(2), 690-6
CODEN: JONRA9; ISSN: 0022-3042
DT Journal
LA English
AB The authors have reported previously that posttreatment with NG-nitro-L-arginine Me ester (L-NAME), an inhibitor of the nitric oxide synthase, reduced the vol. of cortical and striatal infarct induced by middle cerebral artery occlusion in rats. In the present study, the authors investigated the mechanisms by which L-NAME (3 mg/kg i.p.) is neuroprotective in this model of cerebral ischemia. First, the authors have shown the reversal of the neuroprotective effect of L-NAME by a coinjection of L-arginine. Second, in order to det. by which mechanism nitric oxide exacerbates neuronal damage produced by focal cerebral ischemia, the authors studied the effect of the inhibition of nitric oxide synthase by L-NAME on the histol. consequences of a focal injection of N-methyl-D-aspartate (NAMDA) in the striatum, and on the striatal overflow of glutamate and aspartate induced either by K+ depolarization or by focal cerebral ischemia. The authors have found that L-NAME treatment reduced the excitotoxic damage produced by NMDA injection. By using microdialysis, the authors have shown that the K+- and the ischemia-induced glutamate efflux was reduced by 52 and 30%, resp., after the L-NAME treatment. These results indicate that nitric oxide synthesis induced by the NMDA receptor overstimulation is one of the major events leading to neuronal damage. One possible mechanism by which nitric oxide may contribute to the excitotoxic process is by facilitating the ischemia-induced glutamate overflow.
IT **74-79-3**, L-**Arginine**, biological studies
RL: BIOL (Biological study)
(brain ischemia neuroprotective activity of nitro-L-**arginine** Me ester reversal by)
IT **125978-95-2**, **Nitric oxide synthase**
RL: BIOL (Biological study)
(inhibitor of, nitro-L-**arginine** Me ester as, brain ischemia neuroprotective activity of)
CC 1-8 (Pharmacology)
Section cross-reference(s): 14
ST brain ischemia **nitric oxide synthase** inhibitor; methylaspartate brain injury nitric oxide; glutamate release brain injury methylaspartate
IT Cytoprotective agents

(nitro-L-**arginine** Me ester as, in brain ischemia, glutamate release and nitric oxide in)

IT **Brain, disease**
(injury, from methylaspartate, nitro-L-**arginine** Me ester **treatment** of, glutamate release and nitric oxide in)

IT **Brain, disease**
(ischemia, **treatment** of, by nitro-L-**arginine** Me ester, nitric oxide in)

IT 6384-92-5, N-Methyl-D-aspartic acid
RL: BIOL (Biological study)
(brain injury from, nitro-L-**arginine** Me ester **treatment** of, glutamate release and nitric oxide in)

IT **74-79-3**, L-**Arginine**, biological studies
RL: BIOL (Biological study)
(brain ischemia neuroprotective activity of nitro-L-**arginine** Me ester reversal by)

IT 50903-99-6
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(brain ischemia neuroprotective activity of, as **nitric oxide synthase** inhibitor)

IT 10102-43-9, Nitric oxide, biological studies
RL: BIOL (Biological study)
(in brain injury from methylaspartate, nitro-L-**arginine** Me ester **treatment** in)

IT **125978-95-2**, **Nitric oxide synthase**
RL: BIOL (Biological study)
(inhibitor of, nitro-L-**arginine** Me ester as, brain ischemia neuroprotective activity of)

IT 56-84-8, Aspartic acid, biological studies 56-86-0, Glutamic acid, biological studies
RL: BIOL (Biological study)
(release of, in brain injury from methylaspartate, nitro-L-**arginine** Me ester **treatment** in)

L35 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 1997 ACS
AN 1993:462692 HCAPLUS
DN 119:62692
TI Blockade of nitric oxide synthesis: A new pharmacological approach for the **treatment** of cerebral infarction?
AU Nowicki, J. P.; Carreau, A.; Duval, D.; Poignet, H.; Vige, X.; Scatton, B.
CS Biol. Dep., Synthelab. Rech., Bagneux, 92220, Fr.
SO Pharmacol. Cereb. Ischemia 1992, [Int. Symp.], 4th (1992), 409-16.
Editor(s): Krieglstein, Josef; Oberpichler-Schwenk, Heike.
Publisher: Wiss. Verlagsges., Stuttgart, Germany.
CODEN: 59ANAV
DT Conference
LA English
AB The present study clearly demonstrates that L-NNA can greatly reduce the size of the infarct induced by a focal cerebral ischemia in the mouse. Although the precise mechanism by which L-NNA exerts its neuroprotective effects remains to be fully elucidated, the results strongly support a neuronal site of action through the inhibition of NO synthase. Antagonism of NO synthesis might thus represent an important novel pharmacol. approach in the pharmacotherapy of focal brain ischemia.

IT **125978-95-2, Nitric oxide synthase**
RL: PROC (Process)
(inhibition of, by nitroarginine, in cerebral infarction **treatment**)
CC 1-8 (Pharmacology)
IT **Brain, disease**
(infarction, nitroarginine for **treatment** of, **nitric oxide synthase** inhibition in)
IT 2149-70-4, NG-Nitro-L-**arginine**
RL: BIOL (Biological study)
(cerebral infarction **treatment** with, **nitric oxide synthase** inhibition in)
IT **125978-95-2, Nitric oxide synthase**
RL: PROC (Process)
(inhibition of, by nitroarginine, in cerebral infarction **treatment**)

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(FILE 'WPIDS' ENTERED AT 10:56:23 ON 02 OCT 1997)

	DEL	HIS	Y	
L1	9	S		HMG COA REDUCASE OR HMGCOA REDUCTASE#
L2	425	S		HMG COA REDUCTASE# OR HMGCOA REDUCTASE#
L3	1	S		ARGINING
L4	3093	S		ARGININE
L5	1	S		L2 AND L4
L6	122	S		NO SYNTHASE OR NITRIC OXIDE SYNTHASE
L7	172	S		LOVASTATIN OR PRAVASTATIN OR SIMVASTATIN OR FLUVASTATIN
L8	0	S		L4 AND L7
L9	84	S		L6 (5A) (AGONIST# OR INHIBIT?)
L10	36	S		L6 AND L4
L11	41501	S		VASODILAT? OR VASOCONSTR? OR VASORELAX? OR RENOVASCUL?
L12	11	S		L10 AND L11

FILE 'WPIDS' ENTERED AT 11:04:34 ON 02 OCT 1997

=> d .wp 1-11

L12 ANSWER 1 OF 11 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 97-179256 [16] WPIDS
DNC C97-057750
TI Producing NOS from recombinant prokaryotic host cells - provides large amounts of NOS, useful for screening inhibitors to reduce adverse effects of nitric acid formation e.g. neuro degeneration.
DC B04 D16
IN MASTERS, B S; ROMAN, L J; SHETA, E A
PA (TEXA) UNIV TEXAS SYSTEM
CYC 69
PI WO 9708299 A1 970306 (9716)* EN 54 pp
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AM AT AU BB BG CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN
AU 9669102 A 970319 (9728)
ADT WO 9708299 A1 WO 96-US14045 960823; AU 9669102 A AU 96-69102 960823
FDT AU 9669102 A Based on WO 9708299
PRAI US 95-519105 950824
AB WO 9708299 A UPAB: 970417
Recombinant prokaryotic host cells (I) which are protease-deficient and comprise nucleotide sequences encoding **nitric oxide synthase** (NOS) and a folding agonist (or chaperonin), are new. Also claimed are: (1) a method of producing NOS by obtaining (I) and isolating NOS apoenzyme from the cells; (2) the apoenzyme produced by the method of (1); and (3) a protease-deficient prokaryotic cell comprising an expression vector that contains a first nucleotide sequence that encodes a selected protein other than NOS, and a folding agonist.

USE - NOS catalyses the formation of nitric oxide which has many physiological roles e.g. relaxing isolated blood vessels, neurotransmission and neurodegeneration associated with decreased blood flow in AIDS, dementia and Parkinson's disease. Inhibition of NOS action can therefore be advantageous and a NOS source allows screening for inhibitors and drug design. The expression system is also useful for site-directed mutagenesis of NOS and investigation of the role of BH4 in NOS function.

ADVANTAGE - The method allows fast and inexpensive production of large quantities of NOS (average yields of 125-150 nmol enzyme/l of cells) compared with prior art purification or cell culture methods. The co-expression of NOS with chaperonins reduces aggregation, insolubility and proteolysis. The enzyme is as active as that from a mammalian source and may be reactivated by the addition of cofactors e.g. in the presence of BH4 a conversion assay of L-**arginine** to L-citrulline showed enzymatic activities of 239 and 468 compared with 300-450 nmol/min/mg for nNOS purified from human **kidney** 293 cells.
Dwg.0/5

L12 ANSWER 2 OF 11 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 96-425364 [42] WPIDS
DNC C96-134042
TI New L-**arginine** derivs. are **nitric oxide synthase** inhibitors - useful in treating nervous system, gastrointestinal, urinary, **cardiovascular** and broncho-pulmonary disorders.
DC B03 B05

IN BROQUET, C; CHABRIER, DE LASSAUNIERE P
PA (SCRC) SCRAS SOC CONSEILS RECH APPL SCI
CYC 70
PI WO 9627593 A1 960912 (9642)* FR 30 pp
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN
AU 9649479 A 960923 (9702)
ADT WO 9627593 A1 WO 96-FR337 960304; AU 9649479 A AU 96-49479 960304
FDT AU 9649479 A Based on WO 9627593
PRAI GB 95-4350 950304
AB WO 9627593 A UPAB: 961021
Use of L-**arginine** derivs. of formula (I) and their salts in the prepn. of a medicament for treating gastrointestinal or urinary system dysfunction which may or may not be inflammatory is new. A = H, lower alkyl or nitro; E = O or bond; n = 0-12; R1, R2 = alkyl; or NR1R2 = opt. satd. 5 or 6 membered ring of formula (c); X = H (sic), S, N, imino, alkylimino or methylene. Also claimed are: (a) the use of at least one cpd. (I) or one of its salts as an active ingredient in pharmaceutical compsns., excluding cpds. where n = zero, E = bond, A = H and R1, R2 = lower alkyl ; and (b) cpds. (I) where n = zero, E = bond and either: (i) A = H and R1, R2 = alkyl or R1+R2 = imidazole, morpholine or piperidine ring; or (ii) A = nitro and R1+R2 = piperidine ring.

USE - (I) are **nitric oxide synthase** inhibitors for use as immunosuppressants or analgesics, hypotensives or antibacterial, antiarteriosclerotic, vasotropic, antimigraine, opthalmological or antidiabetic agents useful in the treatment of central or peripheral nervous disorders (e.g. cerebral infarctus, migraine, headaches, epilepsy, cerebral or spinal cord trauma, neurodegenerative and/or autoimmune disease such as Alzheimer's or Parkinson's disease, Huntington's chorea, lateral amyotrophic sclerosis, infectious cerebral neuropathies (AIDS), acute and chronic pain, morphine tolerance and dependence, ocular neuropathy and depression). (I) may also be used in treating gastrointestinal and urinary dysfunctions which may be inflammatory (e.g. ulcerous colitis, Crohn's disease, diarrhoea), as well as cardiac and pulmonary system disorders (e.g. atherosclerosis, pulmonary fibrosis, sclerodermia, asthma, septic shock). Admin. is e.g. oral or parenteral and in a daily dosage of 0.1-100 0 (pref. 1-100) mg. Dwg.0/0

L12 ANSWER 3 OF 11 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 96-259550 [26] WPIDS
DNC C96-082130
TI New 2-imino-aza cycloalkane derivs. - are **nitric oxide synthase** inhibitors and are useful for treating e.g. **hypertension**, septic shock, toxic shock syndrome, tuberculosis, cancer etc..
DC B02 B03
IN CALDWELL, C G; DURETTE, P L; GRANT, S K; GUTHIKONDA, R N; MACCOSS, M; SHAH, S K; SHANKARAN, K
PA (MERI) MERCK & CO INC
CYC 65
PI WO 9614844 A1 960523 (9626)* EN 279 pp
RW: AT BE CH DE DK ES FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG

W: AL AM AU BB BG BR BY CA CN CZ EE FI GE HU IS JP KG KR KZ LK LR LT LV MD MG MK MN MX NO NZ PL RO RU SG SI SK TJ TM TT UA US UZ

AU 9644624 A 960606 (9637)
US 5629322 A 970513 (9725) 37 pp
EP 789571 A1 970820 (9738) EN
R: BE DE DK FR GB NL

ADT WO 9614844 A1 WO 95-US14812 951113; AU 9644624 A AU 96-44624 951113; US 5629322 A CIP of US 94-339607 941115, US 95-468120 950606; EP 789571 A1 EP 95-943332 951113, WO 95-US14812 951113

FDT AU 9644624 A Based on WO 9614844; EP 789571 A1 Based on WO 9614844

PRAI US 95-468120 950606; US 94-339607 941115

AB WO 9614844 A UPAB: 960705

2-Imino-azacycloalkane derivs. of formula (I) and their tautomers and salts are new. In (I), dashed line is a tautomeric double bond in either position; either R4 or R5a are absent when their N is double bonded; X is CH2, CH12R13, O, S(O)m, NH or 1-6C alkylimino; n is 0-4; m is 0-2; R1-R3, R12 and R13 are e.g. H, 1-12C alkyl, 1-12C alkoxy, alkyl-S(O)m, mono- or di- (1-12C alkyl)amino, 2-13C alkylcarbonyl; or 2 of R1-R3 on the same C with optional substits. are 5-7 membered, opt. unsatd. monocyclic ring opt. contg. up to 3 N, O or S; or when one of R1-R3 and opt. substits. is attached to C atom next to NR4 gp., this R with CNR4 is a 5-7 membered opt. unsatd. azamonocyclic ring opt. contg. up to 3 N, O or S with the proviso that R12 and R13 are not both H; R4, R5, R5a are H, 1-12C alkyl (opt. contg. 1 or 2 OH, COOH, NR6R7, OR6, COOR6 etc.; and R6 and R7 are H, phenyl, cyclohexyl or 1-6C alkyl.

USE - (I) are **nitric oxide synthase** (NOS) inhibitors and reduce NO prodn. from breakdown of L-**arginine**. (I) are useful in cytokine (induction therapy) for short term immunosuppression in transplant therapy, in treatment of neurodegenerative or gastrointestinal motility disorders and inflammations e.g. **hypertension**, septic shock, toxic shock syndrome, tuberculosis, cancer, cachexia, sunburn, eczema, psoriasis, bronchitis, asthma, ARDS etc.

Dwg.0/0

L12 ANSWER 4 OF 11 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD

AN 96-209574 [21] WPIDS

DNC C96-066863

TI Formulation for **vasorelaxation** or **vasodilation**, useful in treating **cardiovascular** diseases - comprises nitroglycerin and L-**arginine** to stimulate nitric oxide synthesis.

DC B05 B07

IN KAESEMEYER, W H

PA (KAES-I) KAESEMEYER W H

CYC 65

PI WO 9610910 A1 960418 (9621)* EN 40 pp
RW: AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ UG
W: AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LT LU LV MD MG MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TT UA UG UZ VN

AU 9538896 A 960502 (9632)
US 5543430 A 960806 (9637) 16 pp
EP 784429 A1 970723 (9734) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

ADT WO 9610910 A1 WO 95-US12780 951005; AU 9538896 A AU 95-38896 951005;

US 5543430 A US 94-321051 941005; EP 784429 A1 EP 95-938157 951005, WO 95-US12780 951005
FDT AU 9538896 A Based on WO 9610910; EP 784429 A1 Based on WO 9610910
PRAI US 94-321051 941005
AB WO 9610910 A UPAB: 960529
Prevention or treatment of a disease by **vasodilation** or **vasorelaxation** comprises: (i) admin. of a formulation contg. a mixt. of a venous dilator and an arterial dilator; (ii) obtaining periodic indicators of **vasorelaxations**; and (iii) continuing admin. to attain the desired state of **vasorelaxation**. Also claimed is a therapeutic mixt. comprising L-**arginine** and a **nitric oxide synthase** agonist.

USE - The disease to be treated or prevented is **hypertension**, **hypertensive heart** disease, **coronary heart** disease, **cardiovascular** disease, **cerebrovascular** disease or **renovascular** ischaemia (all claimed). The formulations have a combined arterial and venous dilatory effect and can be used to ameliorate or avoid tachycardia, to treat or prevent ischaemia, to prevent reperfusion injury and to treat a wide range of **cardiovascular** diseases (e.g. unstable angina, vasospastic angina, silent ischaemia, perioperative **hypertension**, epicardial **coronary** atherosclerosis, acute myocardial infarction, hibernating and myocardium, sudden death, **heart** failure, stroke and peripheral vascular disease). The formulation may also be used as a cardioplegic soln. to prevent myocardial injury during **coronary** bypass or other open **heart** surgery. Admin. may be intravenous, buccal, intracoronary, intramuscular, rectal, sublingual, oral, subcutaneous or by patch.

ADVANTAGE - Use of a mixt. of dilators relieves **vasoconstriction** by stimulating the constitutive form of **nitric oxide synthase** to produce native nitric oxide, which has enhanced ability to reduce clinical endpoints and mortality cf. exogenous NO produced by an L-**arginine**-independent pathway. The mixt. overcomes nitroglycerin tolerance and reduces the L-**arginine** dosage requirement with its corresp. deleterious consequences of vol. overload.

Dwg.0/4

L12 ANSWER 5 OF 11 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 96-049591 [05] WPIDS
DNC C96-016197
TI New enzyme inhibitors used to treat auto-immune and/or inflammatory disorders - e.g. rheumatoid or osteoarthritis, gastritis, asthma, myocarditis, multiple sclerosis, diabetes, etc..
DC B05
IN CLARK, H A R; DAVIES, P I; DRYSDALE, M J; FRANZMANN, K W; HODSON, H F; KNOWLES, R G; PALMER, R M J; SAWYER, D A; SHEARER, B G; SMITH, S; CLARK, H A; DAVIES, P; FRANZMANN, K
PA (WELL) WELLCOME FOUND LTD
CYC 66
PI WO 9534534 A1 951221 (9605)* EN 35 pp
RW: AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ UG
W: AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LT LU LV MD MG MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TT UA US UZ VN

AU 9528917 A 960105 (9614)
FI 9605019 A 961213 (9711)
NO 9605379 A 961213 (9713)
ZA 9504940 A 970226 (9714) 33 pp
EP 765308 A1 970402 (9718) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
BR 9507995 A 970805 (9738)
ADT WO 9534534 A1 WO 95-GB1378 950614; AU 9528917 A AU 95-28917 950614; FI 9605019 A WO 95-GB1378 950614, FI 96-5019 961213; NO 9605379 A WO 95-GB1378 950614, NO 96-5379 961213; ZA 9504940 A ZA 95-4940 950614; EP 765308 A1 EP 95-924405 950614, WO 95-GB1378 950614; BR 9507995 A BR 95-7995 950614, WO 95-GB1378 950614
FDT AU 9528917 A Based on WO 9534534; EP 765308 A1 Based on WO 9534534; BR 9507995 A Based on WO 9534534
PRAI GB 95-9774 950515; EP 94-304314 940615
AB WO 9534534 A UPAB: 960205
Enzyme inhibitors of formula (I) and their salts, amides, esters and prodrugs are new: R1 = 1-6 C alkyl, 2-6 C alkenyl, 2-6 C alkynyl, 3-6 C cycloalkyl or 3-6 C cycloalkyl (1-6 C) alkyl, each opt. substd. by 1-3 halo, CN, NO2, COR2, S(O)mR6, PO(OR9)2, NR10R11, or OR14; R2 = H, 1-6 C alkyl, OR3 or NR4R5; R3-R5 = H or 1-6 C alkyl; R6 = H, 1-6 C alkyl, OH or NR7R8; m = 0-2; R7, R8 = H or 1-6 C alkyl; R9 = H or 1-6 C alkyl; R10, R11 = H, 1-6 C alkyl, COR12 or S(O)m'R13; R12, R13 = H or 1-6 C alkyl; m' = 0-2; R14 = H, 1-6 C alkyl (opt. substd. by 1-3 halo), 6-10 C aryl, or COR15; and R15 = H or 1-6 C alkyl; p = 2 or 3; q = 1 or 2; and n = 0 or 1.

USE - (I) are used in the mfr. of a medicament used to treat conditions where there is an advantage in inhibiting nitric oxide prodn. from **arginine** by action of **NO synthase** (claimed). (I) are used to treat autoimmune and/or inflammatory diseases e.g. of the joint (e.g. rheumatoid and osteoarthritis), of the gastrointestinal tract (e.g. ulcerative colitis, inflammatory bowel diseases, gastritis and mucosal inflammation), of the lung (e.g. adult respiratory distress syndrome, asthma), of the **heart** (e.g. myocarditis), of the nervous tissue (e.g. multiple sclerosis), of the pancreas (e.g. diabetes mellitus), of the **kidney** (e.g. glomerulonephritis), of the skin (e.g. dermatitis, psoriasis, urticaria), of transplanted organs (e.g. rejection) and multi-organ diseases (e.g. systemic lupus erythematosus). (I) are also used to treat CNS trauma, epilepsy, AIDS dementia, chronic neurodegenerative diseases and chronic pain, priapism, obesity and hyperphagia. Admin. is oral, parenteral, rectal or topical. Oral or injection dose is 0.1-1500 (0.1-500) mg/kg/day.
Dwg.0/0

L12 ANSWER 6 OF 11 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 95-200183 [26] WPIDS
CR 95-067156 [09]
DNC C95-092504
TI Use of nitric oxide substrate and/or donor opt. with a progestin - to treat climacteric disorders during menopause e.g. hot flushes, or to treat **hypertension**.
DC B05
IN BUKOWSKI, R; CHWALISZ, K; GARFIELD, R E; YALLAMPALLI, C
PA (SCHD) SCHERING AG; (GARF-I) GARFIELD R E; (YALL-I) YALLAMPALLI C; (GARF-I) GARFIELD R
CYC 26
PI WO 9513800 A1 950526 (9526)* EN 28 pp

AU 9481446 A 950606 (9538)
NO 9601994 A 960716 (9638)
EP 730445 A1 960911 (9641) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
FI 9602110 A 960715 (9641)
CZ 9601400 A3 960911 (9643)
BR 9408062 A 961224 (9706)
US 5595970 A 970121 (9710) 6 pp
HU 74459 T 961230 (9714)
SK 9600634 A3 970305 (9729)
JP 09505069 W 970520 (9730) 48 pp

ADT WO 9513800 A1 WO 94-EP3818 941117; AU 9481446 A AU 94-81446 941117; NO 9601994 A WO 94-EP3818 941117, NO 96-1994 960515; EP 730445 A1 WO 94-EP3818 941117, EP 95-900760 941117; FI 9602110 A WO 94-EP3818 941117, FI 96-2110 960517; CZ 9601400 A3 CZ 96-1400 941117; BR 9408062 A BR 94-8062 941117, WO 94-EP3818 941117; US 5595970 A CIP of US 93-92426 930716, US 93-153345 931116; HU 74459 T WO 94-EP3818 941117, HU 96-1301 941117; SK 9600634 A3 WO 94-EP3818 941117, SK 96-634 941117; JP 09505069 W WO 94-EP3818 941117, JP 95-514225 941117

FDT AU 9481446 A Based on WO 9513800; EP 730445 A1 Based on WO 9513800; BR 9408062 A Based on WO 9513800; HU 74459 T Based on WO 9513800; JP 09505069 W Based on WO 9513800

PRAI US 93-153345 931116; US 93-92426 930716

AB WO 9513800 A UPAB: 970313

Use of (a) **nitric oxide synthase** substrate, (b) a nitric oxide donor, or both, and, opt. also (d) a progestin or, when the mammal is female, both of (c) an oestrogen and (d) a progestin for mfr. of a medicament for treating climacterium (climacteric symptoms) in a non-pregnant female or in a male mammal is claimed.

The nitric oxide substrate is L-**arginine**. The nitric oxide donor is e.g. sodium nitroprusside, nitroglycerin, glyceryl trinitrate etc.. he oestrogen is estradiol valerate, conjugated equine estrogens, AB-estradiol, estrone or estriol. The progestin is e.g. progesterone, dydrogesterone, medroxyprogesterone etc..

Also claimed is a pharmaceutical compsn. comprising an admixture of (a), (b) or both, and opt. also (c) or (d) with an oestrogen to ameliorate symptoms of climacterium in a menopausal/post menopausal female mammal.

USE - The compsn. can be used to treat and prevent climacteric disorders during menopause, e.g. hot flushes, abnormal clotting patterns, urogenital discomfort, increased incidence of **cardiovascular** diseases, etc. associated with the redn. in ovarian function in middle-aged women. The compsn. can also be used to treat **hypertension** (in males and females), as an adjuvant in contraceptive therapy, thrombotic disorders, menstrual disorders (dysmenorrhea, functional uterine bleeding) and haemorrhage.

Dwg.0/4

L12 ANSWER 7 OF 11 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 95-178551 [23] WPIDS
DNC C95-082632
TI Cyclic amidino derivs. as selective **nitric oxide synthase** inhibitors - are used in cytokine therapy, immunosuppression and transplants, autoimmune or CNS disorders, etc..
DC B03

IN BERGMANIS, A A; CURRIE, M G; FOK, K F; HAGEN, T J; HALLINAN, E A; HANSEN, D W; KRAMER, S W; LEE, L F; METZ, S; MOORE, W M; PETERSON, K B; PITZELE, B S; SPANGLER, D P; TJOENG, F S; TOTH, M V; TRIVEDI, M; WEBBER, R K

PA (SEAR) SEARLE & CO G D

CYC 60

PI WO 9511231 A1 950427 (9523)* EN 237 pp
RW: AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ
W: AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU JP KE KG KP KR KZ LK LR LT LU LV MD MG MN MW NL NO NZ PL PT RO RU SD SE SI SK TJ TT UA US UZ VN
AU 9480811 A 950508 (9533)
NO 9601403 A 960409 (9627)
EP 724570 A1 960807 (9636) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE
JP 09504028 W 970422 (9726) 367 pp

ADT WO 9511231 A1 WO 94-US11832 941020; AU 9480811 A AU 94-80811 941020; NO 9601403 A WO 94-US11832 941020, NO 96-1403 960409; EP 724570 A1 EP 94-931893 941020, WO 94-US11832 941020; JP 09504028 W WO 94-US11832 941020, JP 95-512153 941020

FDT AU 9480811 A Based on WO 9511231; EP 724570 A1 Based on WO 9511231; JP 09504028 W Based on WO 9511231

PRAI US 93-141168 931021

AB WO 9511231 A UPAB: 950619

Pharmaceutical compsn. comprising a cyclic amidine of formula (I), or its salts, esters, and prodrugs, with non-toxic, pharmaceutical carrier(s), is new: X = CH2, N, O, S, SO, or SO2, in which N and lower alkyl radicals are opt. substd. by OH,-1-10C alkyl, haloalkyl, or alkoxy, or amino; n = 0 to about 7; R1, R2 = H, or 1-10C alkyl, alkoxy, alkylthio, or haloalkyl, 2-10C alkenyl or alkynyl, halo, nitro, amino, COOH, CN, sulphonyl, carboalkoxy, carboaryloxy, carboalkylaryloxy, 3-10C alicyclic hydrocarbyl, 4-16C aromatic hydrocarbyl, 4-10C heterocyclyl (opt. fused to an aromatic), CONR5R6, SO2NR5R6, COR5, SO2R5, sulphonamide, alkyl sulphate, or alkyl or aryl sulphoxide or sulphone (all opt. substd. by OH, or 1-10C alkyl, alkoxy, alkylthio, or haloalkyl, 2-10C alkenyl or alkynyl, halo, nitro, amino, COOH, CN, sulphonyl, carboalkoxy, carboaryloxy, carboxyalkylaryloxy, SO2NR5R6 or SO2R5 (all opt. substd. by amino, COOH, carboalkoxy, carboaryloxy, carboxyalkylaryloxy, or 1-10C alkoxy)); or R1R2 together = 3-10C alicyclic hydrocarbyl, 4-16C aromatic hydrocarbyl, or 4-10C heterocyclyl (opt. fused to an aromatic) (all opt. substd. by 1-10C alkyl, or 2-10C alkyl or alkynyl (all opt. substd. by COOH, carboalkoxy, carboaryloxy, carboxyalkylaryloxy, or 1-10C alkoxy); R3, R4 = H, OH, or 1-10C alkoxy; and R5, R6 = H, 1-10C alkyl, or 4-16C aryl; provided that, when n = 1 and R1 and/or R2 are at positions 3 or 4, then neither R1 nor R2 are aryl. Also new are the cpds. (I), including the n = 1 proviso, and also that, (i) when X = CH2, N, O, or S, then R1 and R2 are not both H or haloalkyl; and (ii) when n = 3, then R1 is not 7-Me.

USE - (I) modulate or inhibit **nitric oxide synthase** (NOS) selectively, affecting the inducible but not the constitutive isoform of NOS in NO synthesis from **arginine**. Inhibition of this reaction is of advantage in systemic hypotension from septic and/or toxic shock; therapy with cytokines, e.g., TNF, IL-1, and IL-2; as an adjuvant to short term immunosuppression in transplant therapy; and in autoimmune diseases and/or inflammatory disorders, e.g., those affecting the joints

(arthritis) inflammatory bowel disease, **cardiovascular** or cerebral ischaemia, diabetes, hyperalgesia (allodynia), focal or global ischaemia or thrombotic stroke secondary to cardiac arrest, or CNS disorders mediated by NO.

ADVANTAGE - Prior art NOS inhibitors used in therapy, in partic. L-NMMA, are non-selective, and precautions against serious results from over-inhibition of constitutive NOS, including **hypertension**, possible thrombosis, and tissue damage are necessary, e.g, continuous blood pressure monitoring. (I) are therefore easier to use and more beneficial in therapy.
Dwg.0/1

L12 ANSWER 8 OF 11 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 95-035956 [05] WPIDS
DNC C95-016069
TI Inhibiting development of atherosclerosis or restenosis in humans - by admin. of agents which enhance endogenous nitric oxide levels in the vascular system.
DC B05
IN COOKE, J P; DZAU, V J; GIBBONS, G H
PA (STRD) UNIV LELAND STANFORD JUNIOR
CYC 2
PI WO 9428721 A1 941222 (9505)* EN 35 pp
US 5428070 A 950627 (9531) 8 pp
EP 702518 A1 960327 (9617) EN
JP 08511530 W 961203 (9710) 32 pp
ADT WO 9428721 A1 WO 94-US6203 940602; US 5428070 A US 93-76312 930611; EP 702518 A1 EP 94-918203 940602, WO 94-US6203 940602; JP 08511530 W WO 94-US6203 940602, JP 95-501932 940602
FDT EP 702518 A1 Based on WO 9428721; JP 08511530 W Based on WO 9428721
PRAI US 93-76312 930611; US 94-184519 940121
AB WO 9428721 A UPAB: 950207
The following are claimed: (A) inhibiting the development of (i) atherosclerosis or (ii) restenosis in the vascular system of human hosts susceptible to atherosclerosis or restenosis, comprising admin. of a prophylactic or therapeutic dose of an agent, other than as a natural food source, to enhance the level of endogenous NO in the vascular system. (B) Inhibiting plaque formation in the **cardiovascular** system of human hosts, comprising admin. of a chemical agent, comprising an amine cpd. and an oxidant, capable of reacting in vivo to enhance the level of endothelium-derived relaxing factor in the **cardiovascular** system. (C) Inhibiting plaque formation in the **cardiovascular** system of human hosts, comprising transfecting cells with a genetic construct comprising a gene encoding an enzyme in the biosynthetic pathway to NO. The gene is expressed in the cells and the enzyme is secreted. The cells are either endogenous to the host, or are introduced into the host. The enzyme is secreted to enhance the level of NO in the **cardiovascular** system.

USE - The processes are useful for treatment of, e.g., atherosclerosis, vascular thrombosis, or restenosis.
Dwg.0/4

L12 ANSWER 9 OF 11 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 94-006681 [01] WPIDS
CR 92-268000 [32]; 95-268842 [35]
DNC C94-002601
TI In vitro control of nitric oxide biosynthesis - using physiologically active N6(hydrazino-imino methyl)-lysine to inhibit

nitric oxide formation from **arginine**, useful for treating e.g. shock, hypotension etc..

DC B05
IN GRIFFITH, O W
PA (CORR) CORNELL RES FOUND INC
CYC 1
PI US 5273875 A 931228 (9401)* 10 pp
ADT US 5273875 A Div ex US 91-673831 910322, US 92-865060 920408
FDT US 5273875 A Div ex US 5132453
PRAI US 91-673831 910322; US 92-865060 920408
AB US 5273875 A UPAB: 950918

The biosynthesis, metabolism or physiological role of nitric oxide can be controlled in vitro by adding physiologically active N6(hydrozinoiminomethyl)lysine (I) or one of its acid addn. salts in an amt. sufficient to inhibit nitric oxide formation from **arginine**, to a medium contg. isolated organs, intact cells, cell homogenates or tissue homogenates from mammals.

Pref. media include cardiac perfusion media, tissue culture media, incubation media used with cell or tissue homogenates or purified proteins. The organ treated is typically a blood vessel, lung or **kidney**.

USE/ADVANTAGE - (I) are more selective than N4-methyl-L-**arginine** (NMMA), NG-nitro-L-**arginine** (NNA) and NG-amino-L-**arginine** in inhibiting the inducible isoform of **nitric oxide synthase** than the constitutive isoform of **nitric oxide synthase** and is substantially less toxic than NAA. (I) can be used in vivo for prophylactic and therapeutic purposes e.g. for treating patients with pathologically low blood pressure, idiopathic hypotension, drug induced hypotension, shock, immune disorders in which down regulation of nitric oxide formation is advantageous e.g. auto immune disorders. Suitable doses are 10 micro-g to 100 mg/kg, esp. 1-10 mg/kg.

Dwg.0/3

Dwg.0/3

L12 ANSWER 10 OF 11 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 93-303470 [38] WPIDS
DNC C93-135216
TI Endothelial **nitric oxide synthase** and gene - which catalyses nitric oxide formation, for e.g. inhibiting platelet aggregation or smooth muscle cell proliferation.
DC B04 D16
IN BLOCH, D B; BLOCH, K D; JANSSENS, S P
PA (GEHO) GEN HOSPITAL CORP
CYC 19
PI WO 9318156 A1 930916 (9338)* EN 34 pp
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: AU CA JP
AU 9337891 A 931005 (9405)
ADT WO 9318156 A1 WO 93-US1951 930305; AU 9337891 A AU 93-37891 930305
FDT AU 9337891 A Based on WO 9318156
PRAI US 92-846558 920305; US 93-27071 930304
AB WO 9318156 A UPAB: 931123

(A) A pure prepn. of a nucleic acid comprising a sequence encoding endothelial **nitric oxide synthase** (ECNOS) is claimed.

Also claimed are: (B) a vector comprising the nucleic acid of (A); (C) a cell comprising a vector as in (B); (D) a pure prepn. of

ECNOS; (E) a method of catalysing the formation of nitric oxide comprising contatcing L-**arginine** with a purified prepn. of ECNOS; (F) a method of treating a mammal having **hypertension** comprising administering ECNOS.

USE - The ECNOS can be used for treating a vascular or circulatory disorder, e.g. systemic or pulmonary **hypertension**, accelerated-atherosclerosis associated with angioplasty or **coronary** artery spasm. The ECNOS nucleic acid can be used for determining the risk of such circulatory disorder. THe ECNOS can also be used for inhibiting or reverseing platelet aggregation or for inhibiting smooth muscle cell proliferation. Inhibitors of ECNOS can be used as e.g. anti-inflammatory agents while stimulators and agonists are useful for decreasing blood pressure.

Dwg.0/5

L12 ANSWER 11 OF 11 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 93-220590 [28] WPIDS
DNC C93-098206
TI Salts and amide(s) of acidic cyclo-oxygenase inhibitors with L-**arginine** analogues - useful in treatment of **heart** and **cerebrovascular** disorders e.g. migraine, stroke etc., various inflammations and immune disorders.
DC B05
IN AUVIN, S; BRAQUET, P; BROQUET, C; CHABRIER, DE LASSAUNIERE P; DE, LASSAUNIERE P C; CHABRIER, DELAUSSENIERE P; BAQUET, P; BRAQUET, C
PA (SCRC) SCRAS SOC CONSEILS RECH APPL SCI; (SCRC) SOC CONSEILS RECH APPL SCI; (SCRC) SCRAS SOC CONSEILS RECH APPL S; (SCRC) SCRAS SOC CONSEILS RECH & APPL S; (SCRC) SCRAS SOC CONSEILS RECH & APPL SCI; (SCRC) SOC CONSEILS RECH & APPL SCI
CYC 24
PI

DE 4244539	A1	930708	(9328)*		12 pp
GB 2263111	A	930714	(9328)		25 pp
AU 9230498	A	930708	(9334)		
NL 9300001	A	930802	(9334)		29 pp
SE 9203825	A	930705	(9334)		
NO 9204835	A	930705	(9335)		
CA 2085555	A	930705	(9339)		
DK 9201575	A	930705	(9339)		
FI 9205883	A	930705	(9339)		
FR 2685869	A1	930709	(9340)		23 pp
FR 2685916	A1	930709	(9340)		23 pp
LU 88208	A	930415	(9341)	FR	
JP 05286916	A	931102	(9348)		14 pp
ZA 9210080	A	931027	(9348)		23 pp
HU 64047	T	931129	(9401)		
PT 101165	A	940228	(9412)		
BE 1006227	A3	940614	(9427)		25 pp
ES 2052452	A1	940701	(9429)		
US 5360925	A	941101	(9443)		9 pp
ES 2052452	B1	950201	(9511)		
NZ 245499	A	950726	(9535)		
GB 2263111	B	950816	(9536)		
CH 685629	A5	950831	(9539)		
AT 9202560	A	951015	(9546)		
AU 664399	B	951116	(9602)		
US 5480999	A	960102	(9607)		10 pp
TW 267152	A	960101	(9612)		
AT 401054	B	960415	(9620)		

IT 1256761 B 951215 (9628)
IE 71675 B 970226 (9717)

ADT DE 4244539 A1 DE 92-4244539 921230; GB 2263111 A GB 92-27026 921224; AU 9230498 A AU 92-30498 921231; NL 9300001 A NL 93-1 930104; SE 9203825 A SE 92-3825 921218; NO 9204835 A NO 92-4835 921214; CA 2085555 A CA 92-2085555 921216; DK 9201575 A DK 92-1575 921230; FI 9205883 A FI 92-5883 921228; FR 2685869 A1 FR 92-15447 921222; FR 2685916 A1 FR 92-15448 921222; LU 88208 A LU 92-88208 921229; JP 05286916 A JP 93-91 930104; ZA 9210080 A ZA 92-10080 921229; HU 64047 T HU 92-4173 921230; PT 101165 A PT 92-101165 921230; BE 1006227 A3 BE 92-1127 921222; ES 2052452 A1 ES 92-2635 921229; US 5360925 A Div ex US 92-995792 921223, US 93-128908 930929; ES 2052452 B1 ES 92-2635 921229; NZ 245499 A NZ 92-245499 921217; GB 2263111 B GB 92-27026 921224; CH 685629 A5 CH 92-3890 921218; AT 9202560 A AT 92-2560 921223; AU 664399 B AU 92-30498 921231; US 5480999 A US 92-995792 921223; TW 267152 A TW 92-110175 921218; AT 401054 B AT 92-2560 921223; IT 1256761 B IT 92-MI2953 921223; IE 71675 B IE 92-2954 921231

FDT AU 664399 B Previous Publ. AU 9230498; AT 401054 B Previous Publ. AT 9202560

PRAI GB 92-114 920104

AB DE 4244539 A UPAB: 931116

Salts and amides of acidic cyclooxygenase inhibitors with L-forms of **arginine** analogues are of formula AB (I). In (I), A = a cyclooxygenase inhibitor which has an accessible acid function and is of formula RCOOH, in which R is the cyclooxygenase moiety B = the L-form of an **arginine** analogue of formula (B) R1 = H, Me or Et; R2 = H or NO2; R3 = amino, methylamino, ethylamino, hydrazino, Me or Et; provided that if AB is a salt, in which R2 = H, R3 is not amino.

USE/ADVANTAGE - (I) have dual biological activity in that they inhibit both the L-**arginine/NO synthase** and cyclooxygenase pathways and can thus be used in the treatment of **heart** and **cerebrovascular** disorders (eg. migraine, stroke, infarction, ischaemia, sepsis, endotoxic and haermorrhagic shock, pain) various inflammations (eg. acute rheumatic fever, rheumatoid arthritis and other types of arthritis, osteroarthrosis and asthma) and immune disorders (eg. viral and non-viral infections, autoimmune disorders, drug abuse, cancer and various pathologies in which excessive prodn. of NO and/or archidonic acid metobolites plays a part). The combination of the two components A and B in one molecule is synergistic.

Dwg.0/0

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=> d his

     (FILE 'MEDLINE' ENTERED AT 13:00:05 ON 02 OCT 1997)
               DEL HIS Y
L1          3051 S LOVASTATIN OR PRAVASTATIN OR SIMVASTATIN OR FLUVASTATIN
L2         18736 S ARGININE/CT
L3             4 S L1 AND L2
               E HYDROXYMETHYLGLUTARYL COA REDUCTASES/CT
L4          2990 S HYDROXYMETHYLGLUTARYL COA REDUCTASES/CT
L5             2 S L4 AND L2

=> d .med l3 1-4;d .med l5 1-2

L3   ANSWER 1 OF 4  MEDLINE
AN   97037871     MEDLINE
TI   Lipids and endothelial function: effects of lipid-lowering and other
     therapeutic interventions.
AU   Luscher T F; Tanner F C; Noll G
CS   Cardiology, Cardiovascular Research, University Hospital, Bern,
     Switzerland.
SO   CURRENT OPINION IN LIPIDOLOGY, (1996 Aug) 7 (4) 234-40.  Ref: 67
     Journal code: B05. ISSN: 0957-9672.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
     General Review; (REVIEW)
     (REVIEW, TUTORIAL)
LA   English
FS   Priority Journals
EM   9704
EW   19970401
AB   Coronary arteries are regulated by neuronal mechanisms, hormones and
     paracrine mediators. The importance of endothelium-dependent
     mechanisms has recently been recognized. The endothelium responds to
     mechanical and chemical signals from the blood by releasing
     mediators that modulate vascular tone and structure, platelet
     function, coagulation and monocyte adhesion. Important relaxing
     factors are nitric oxide, prostacyclin and a putative
     hyperpolarizing factor. Nitric oxide also inhibits smooth muscle
     proliferation and, together with prostacyclin, platelet function.
     Bradykinin-induced nitric oxide production is reduced by
     angiotensin-converting enzyme. Endothelin-1, thromboxane A2 and
     prostaglandin H2 are contracting factors. Thromboxane A2 and
     prostaglandin H2 activate platelets, while endothelin has no direct
     platelet effects, but causes smooth muscle proliferation. In
     hypercholestermia, endothelium-dependent relaxation is impaired and
     contraction as well as adhesion of monocytes and platelets enhanced.
     Pharmacological correction of hyperlipidemia by statins also
     improves or normalizes endothelial dysfunction in patients.
     Angiotensin-converting enzyme inhibitors have similar effects.
CT   Check Tags: Animal; Human; Support, Non-U.S. Gov't
      Angiotensin-Converting Enzyme Inhibitors: TU, therapeutic use
      Anticholesteremic Agents: TU, therapeutic use
      Arginine: TU, therapeutic use
      Atherosclerosis: PP, physiopathology
      Coronary Vessels: DE, drug effects
      Endothelin-1: GE, genetics
      Endothelin-1: ME, metabolism
     *Endothelin-1: PH, physiology
      Endothelium, Vascular: AB, abnormalities
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Endothelium, Vascular: DE, drug effects
*Endothelium, Vascular: PH, physiology
Hyperlipidemia: DT, drug therapy
Hyperlipidemia: PP, physiopathology
*Lipids: PH, physiology
Lipoproteins, LDL: PH, physiology
Lovastatin: TU, therapeutic use
Nitric Oxide: AI, antagonists & inhibitors
Nitric Oxide: BI, biosynthesis
*Nitric Oxide: PH, physiology
Swine

COLJ-EE2 Zn glu
Zn aspartate

L3 ANSWER 2 OF 4 MEDLINE
AN 95364506 MEDLINE
TI Vascular function in the forearm of hypercholesterolaemic patients off and on lipid-lowering medication.
AU Stroes E S; Koomans H A; de Bruin T W; Rabelink T J
CS Department of Nephrology, University Hospital Utrecht, The Netherlands.
SO LANCET, (1995 Aug 19) 346 (8973) 467-71.
Journal code: L0S. ISSN: 0140-6736.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 9511
AB To study whether vascular dysfunction in hypercholesterolaemia is reversible, we investigated patients without overt arterial disease who were taking maintenance treatment for hypercholesterolaemia. Medication was stopped for 2 weeks, reinstituted for 12 weeks, and again stopped for 6 weeks. During both maintenance treatment and the 12 weeks of step-up medication the lipid profile was improved but did not return to normal. Dose-response curves for serotonin-induced vasodilatation, an index of nitric oxide-dependent vasodilatation, showed a comparable and significant rightward shift after a medication-free period of 2 and 6 weeks compared with control subjects, indicating endothelial dysfunction, which was already maximum after 2 weeks. After 12 weeks of lipid-lowering medication, the difference in endothelial function between controls and patients had disappeared. Co-infusion of L-arginine, the substrate for nitric oxide synthase, returned the impaired serotonin response during hypercholesterolaemia to normal, but had no effect on this response in controls or in patients while on lipid-lowering medication. Neither endothelium-independent vasorelaxation, assessed by sodium nitroprusside infusion, nor vasoconstriction induced by the nitric oxide blocker L-NMMA, were different between controls and patients, whether the latter were on or off lipid-lowering medication. Our results show an L-arginine-sensitive, impaired nitric-oxide-mediated vascular relaxation of forearm resistance vessels in hypercholesterolaemia which is reproducible, and reversible after short-term lipid-lowering therapy. Demonstration of such changes in this readily accessible vascular bed will allow larger trials assessing vascular function during lipid-lowering therapy to be done.
CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Adult
*Antilipemic Agents: TU, therapeutic use
Arginine: AA, analogs & derivatives
Arginine: AD, administration & dosage

Arginine: PD, pharmacology
Blood Pressure
Cholesterol: BL, blood
*Cholestyramine: TU, therapeutic use
Dose-Response Relationship, Drug
Drug Therapy, Combination
*Forearm: BS, blood supply
*Hypercholesterolemia, Familial: DT, drug therapy
*Hypercholesterolemia, Familial: PP, physiopathology
Infusions, Intravenous
***Lovastatin: AA, analogs & derivatives**
Lovastatin: TU, therapeutic use
Nitroprusside: AD, administration & dosage
Nitroprusside: PD, pharmacology
Regional Blood Flow: PH, physiology
Serotonin: AD, administration & dosage
Serotonin: PD, pharmacology
Vasodilation: DE, drug effects
Vasodilation: PH, physiology

L3 ANSWER 3 OF 4 MEDLINE
AN 93271103 MEDLINE
TI Decreased basal nitric oxide release in hypercholesterolemia increases neutrophil adherence to rabbit coronary artery endothelium.
AU Lefer A M; Ma X L
CS Department of Physiology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pa. 19107-6799.
NC GM-45434 (NIGMS)
SO ARTERIOSCLEROSIS AND THROMBOSIS, (1993 Jun) 13 (6) 771-6.
Journal code: AZ1. ISSN: 1049-8834.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9309
AB Hypercholesterolemia, before atherosclerosis, is known to reduce agonist- (e.g., acetylcholine) mediated nitric oxide (NO) production within 2 weeks of a cholesterol-enriched diet. However, no data exist on the effect of hypercholesterolemia on the basal release of NO from blood vessels. We studied the basal release of NO in rabbit coronary arteries by addition of the NO synthase blocker NG-nitro-L-arginine-methyl ester (L-NAME). Basal release of NO was markedly attenuated 2 weeks after introduction of a 0.5% cholesterol addition to the diet. One week later, the adherence of neutrophils to the coronary endothelium was significantly enhanced (i.e., threefold; $p < 0.01$ different from control). The increased adhesiveness could be attributed to enhanced endothelial adhesion rather than to changes in the properties of the leukocytes. Both phenomena could be reversed by addition of L-arginine to isolated coronary arteries. Administration of 10 mg/day **lovastatin**, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, markedly attenuated both the reduced basal NO production and the increased adhesiveness of the endothelium. These results support the concept that NO is an important protective agent produced by the endothelium to preserve the integrity of the endothelium and may protect it against atherogenesis.
CT Check Tags: Animal; Male; Support, U.S. Gov't, P.H.S.
Amino Acid Oxidoreductases: AI, antagonists & inhibitors

Arginine: AA, analogs & derivatives
Arginine: PD, pharmacology
Cell Adhesion: DE, drug effects
Cholesterol, Dietary: PD, pharmacology
Coronary Vessels
*Endothelium, Vascular: CY, cytology
*Hypercholesterolemia: ME, metabolism
Lovastatin: PD, pharmacology
*Neutrophils: CY, cytology
*Nitric Oxide: ME, metabolism
Rabbits

L3 ANSWER 4 OF 4 MEDLINE
AN 92031349 MEDLINE
TI Hypercholesterolemia and atherosclerosis change vascular reactivity in rabbits by different mechanisms.
AU Galle J; Busse R; Bassenge E
CS Department of Applied Physiology, University of Freiburg, FRG.
SO ARTERIOSCLEROSIS AND THROMBOSIS, (1991 Nov-Dec) 11 (6) 1712-8. Journal code: AZ1. ISSN: 1049-8834.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9202
AB Vasomotor reactivity was assessed in vitro in arterial segments obtained from rabbits with different stages of atherosclerosis. Rabbits were fed a standard chow diet (controls) or a cholesterol-enriched diet to induce hypercholesterolemia and atherosclerosis. A third group received the hydroxymethylglutaryl coenzyme A reductase inhibitor, **lovastatin**, simultaneously with the cholesterol diet. Contractile responses of thoracic aortas to norepinephrine, serotonin, and potassium-rich solution, as well as endothelium-dependent dilations to acetylcholine, were compared after 2 and 4 months on the respective diet. Additionally, plasma cholesterol levels and the amount of plaques covering the intimal surface (as a percentage of the intimal surface) were determined; transmission electron microscopy of atherosclerotic arteries was also performed. After 2 months, the only difference was an enhancement of contractile responses to serotonin in the cholesterol-fed versus the control group. After 4 months on the diet, contractile responses to serotonin were further enhanced, and norepinephrine- and potassium-induced vasoconstrictions were now also significantly enhanced in cholesterol-fed animals versus controls. Endothelium-dependent vasodilations were simultaneously reduced in cholesterol-fed animals. These alterations were partly prevented in cholesterol-fed and **lovastatin**-treated animals. Suppression of nitric oxide synthesis in control aortas by NG-nitro-L-arginine did not reveal any significant increases in contractile responses. Contractile responses to serotonin were enhanced after 2 months on the diet but before the appearance of intimal plaques, whereas attenuation of endothelium-dependent dilations, as well as the further enhancement of contractile responses to serotonin and to other agonists, were closely correlated with the degree of intimal plaques after 4 months on the diet.(ABSTRACT TRUNCATED AT 250 WORDS)
CT Check Tags: Animal; Support, Non-U.S. Gov't
Animal Feed
Aorta, Thoracic: PA, pathology

*Aorta, Thoracic: PP, physiopathology
Arginine: AA, analogs & derivatives
Arginine: PD, pharmacology
Atherosclerosis: PA, pathology
*Atherosclerosis: PP, physiopathology
Cholesterol: BL, blood
Endothelium, Vascular: PP, physiopathology
Hypercholesterolemia: BL, blood
*Hypercholesterolemia: PP, physiopathology
Lovastatin: PD, pharmacology
Rabbits
Vasoconstriction: DE, drug effects
Vasoconstrictor Agents: PD, pharmacology
Vasodilation

L5 ANSWER 1 OF 2 MEDLINE
AN 91295598 MEDLINE
TI Identification of a heterozygous compound individual with familial hypercholesterolemia and familial defective apolipoprotein B-100.
AU Rauh G; Schuster H; Fischer J; Keller C; Wolfram G; Zollner N
CS Medizinische Poliklinik der Universitat Munchen..
SO KLINISCHE WOCHENSCHRIFT, (1991 May 3) 69 (7) 320-4.
Journal code: KWH. ISSN: 0023-2173.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9110
AB Familial defective apolipoprotein B-100 (FDB) is a recently identified dominantly inherited genetic disorder, which leads to increased serum levels of low density lipoprotein (LDL) cholesterol with reduced affinity for the LDL receptor. This genetic disorder is characterized by defective binding of the apolipoprotein B-100 (apo B-100), which is virtually the sole protein constituent of LDL, to the LDL receptor. The defective binding results from a G to A mutation at amino acid 10,708 in exon 26 of the apolipoprotein B (apo B) gene creating a substitution of glutamine for arginine in the codon for amino acid 3500. It is postulated that FDB can exhibit the same clinical features as familial hypercholesterolemia (FH) caused by a defective LDL receptor. The purpose of this paper is to report on an individual with a defective LDL and a defective LDL receptor. The clinical features of this individual were the same as in the family members with either defective LDL or a defective LDL receptor: premature arcus lipoides, tendon xanthomata, and premature atherosclerosis. Although the clinical features were present to the same degree as in individuals with either defect the prognosis and treatment of such an individual could be different.
CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Adolescence
Adult
Aged
*Apolipoproteins B: GE, genetics
Arginine: GE, genetics
Base Sequence
Child
DNA, Circular: GE, genetics
Glutamine: GE, genetics

Heterozygote
Hydroxymethylglutaryl CoA Reductases: IP, isolation & purification
*Hypercholesterolemia, Familial: GE, genetics
*Lipid Metabolism, Inborn Errors: GE, genetics
Middle Age
Molecular Sequence Data
Mutation
Pedigree
Protein Binding

L5 ANSWER 2 OF 2 MEDLINE
AN 87220558 MEDLINE
TI Lysine: arginine ratio of protein and its effect on cholesterol metabolism.
AU Rajamohan T; Kurup P A
SO INDIAN JOURNAL OF BIOCHEMISTRY AND BIOPHYSICS, (1986 Oct) 23 (5) 294-6.
Journal code: GHW. ISSN: 0301-1208.
CY India
DT Journal; Article; (JOURNAL ARTICLE)
LA English
EM 8709
CT Check Tags: Animal; Male
***Arginine: AN, analysis**
*Cholesterol: ME, metabolism
*Cholesterol, Dietary: ME, metabolism
*Dietary Proteins: PD, pharmacology
Hydroxymethylglutaryl CoA Reductases: ME, metabolism
Liver: EN, enzymology
*Lysine: AN, analysis
Rats
Rats, Inbred Strains

=> fil biosis
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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 24 September 1997 (970924/ED)
CAS REGISTRY NUMBERS (R) LAST ADDED: 24 September 1997 (970924/UP)

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(FILE 'BIOSIS' ENTERED AT 13:12:33 ON 02 OCT 1997)

	DEL HIS Y	
L1	710	S (HYDROXYMETHYL(2W) GLUTARYL OR HYDROXY(2W) METHYL(2W) G
L2	2980	S L1 OR HMGCOA OR HMG COA
~~L3~~	~~0~~	~~S ARGINEN~~
L4	46394	S ARGININE
L5	7	S L2 AND L4
L6	3438	S LOVASTATIN OR PRAVASTATIN OR SIMVASTATIN OR FLUVASTATIN
L7	13	S L6 AND L4
L8	6	S L5 NOT L7

FILE 'BIOSIS' ENTERED AT 13:19:54 ON 02 OCT 1997

=> d bib ab l7 1-13;d bib ab l8 16

L7 ANSWER 1 OF 13 BIOSIS COPYRIGHT 1997 BIOSIS
AN 97:411182 BIOSIS
DN 99703225
TI Dietary L-**arginine** reduces the progression of atherosclerosis in cholesterol-fed rabbits: Comparison with **lovastatin**.
AU Boeger R H; Bode-Boeger S M; Brandes R P; Phivthong-Ngam L; Boehme M; Nafe R; Muegge A; Froelich J C
CS Inst. Clinical Pharmacol., Hannover Med. Sch., Konstanty-Gutschow-Str. 8, 30625 Hannover, Germany
SO Circulation 96 (4). 1997. 1282-1290. ISSN: 0009-7322
LA English
AB Background. We investigated whether L-**arginine** induces regression of preexisting atheromatous lesions and reversal of endothelial dysfunction in hypercholesterolemic rabbits, whether similar effects can be obtained by cholesterol-lowering therapy with **lovastatin**, and which mechanism leads to these effects. Methods and Results. Rabbits were fed 1% cholesterol for 4 weeks and 0.5% cholesterol for an additional 12 weeks. Two groups of cholesterol-fed rabbits were treated with L-**arginine** (2.0% in drinking water) or **lovastatin** (10 mg/d) during weeks 5 through 16. Systemic nitric oxide (NO) formation was assessed as the urinary excretion rates of nitrate and cGMP in weekly intervals. Cholesterol feeding progressively reduced urinary nitrate excretion to apprxeq 40% of baseline (P lt .05) and increased plasma concentrations of asymmetrical dimethylarginine (ADMA), an endogenous NO synthesis inhibitor. Dietary L-**arginine** reversed the reduction in plasma L-**arginine**/ADMA ratio and partly restored urinary excretion of nitrate and cGMP (each P lt .05 vs cholesterol) but did not change plasma cholesterol levels. L-**Arginine** completely blocked the progression of carotid intimal Plaques, reduced aortic intimal thickening, and preserved endothelium-dependent vasodilator function. **Lovastatin** treatment reduced plasma cholesterol by 32% but did not improve urinary nitrate or cGMP excretion or endothelium-dependent vasodilation. **Lovastatin** had a weaker inhibitory effect on carotid plaque formation and aortic intimal thickening than L-**arginine**. L-**Arginine** inhibited but **lovastatin** potentiated superoxide radical generation in the atherosclerotic vascular wall. Conclusions. Dietary L-**arginine** improves NO-dependent vasodilator function in cholesterol-fed rabbits and completely blocks the progression of plaques via restoration of NO synthase substrate availability and reduction of vascular oxidative stress. **Lovastatin** treatment has a weaker inhibitory effect on the progression of atherosclerosis and no effect on vascular NO elaboration, which may be due to its stimulatory effect on vascular superoxide radical generation.

L7 ANSWER 2 OF 13 BIOSIS COPYRIGHT 1997 BIOSIS
AN 97:161833 BIOSIS
DN 99461036
TI **Simvastatin**, an HMG-coenzyme A reductase inhibitor, improves endothelial function within 1 month.
AU O'Driscoll G; Green D; Taylor R R

CS Dep. Cardiol., Royal Perth Hosp., Wellington St., Perth 6000, Western Australia
SO Circulation 95 (5). 1997. 1126-1131. ISSN: 0009-7322
LA English
AB Background. Cholesterol-lowering therapy can improve cardiovascular morbidity and mortality in patients with atherosclerosis. Although the mechanisms responsible are unclear, these benefits precede macroscopic changes in the vasculature. Emerging evidence that improvement in endothelial function may occur requires substantiation; in particular, it is unclear how early any such improvement would be detectable after initiation of therapy. Methods and Results. This randomized, double-blind, placebo-controlled crossover study evaluated the effect of **simvastatin** (20 mg daily for 4 weeks) on endothelium-dependent and endothelium-independent vasodilation and on the response to the inhibitor of nitric oxide synthesis, N-G-monomethyl-L-**arginine** (L-NMMA), in the forearm vasculature of subjects with moderate elevation of total serum cholesterol (6.0 to 10.0 mmol/L) by use of strain-gauge plethysmography. Studies were repeated after 3 more months of open therapy. When the results are expressed as percentage changes in flow in the infused arm relative to the noninfused arm, the vasodilator response to acetylcholine was significantly increased after 4 weeks of treatment with **simvastatin** (P lt .0005), and this improvement was further enhanced after 3 months (P lt .005). Concurrently, **simvastatin** augmented the vasoconstrictor response to L-NMMA, an effect that was maintained at 3 months (P lt .0005). The response to the endothelium-independent vasodilator sodium nitroprusside was unaltered. Conclusions. These observations indicate that within 1 month of treatment with **simvastatin**, both the stimulated and basal nitric oxide dilator functions of the endothelium are augmented, and the benefits of this HMG-coenzyme A reductase inhibitor persist with continued therapy.

L7 ANSWER 3 OF 13 BIOSIS COPYRIGHT 1997 BIOSIS
AN 96:454536 BIOSIS
DN 99176892
TI L-**arginine** improves endothelial vasodilator function and slows the progression, but does not induce regression of atherosclerosis in cholesterol-fed rabbits: Comparison with **lovastatin**.
AU Phivthong-Ngam L; Bode-Boeger S M; Boeger R H; Boehme M; Brandes R P; Muegge A; Froelich J C
CS Inst. Clin. Pharmacol., Med. Sch., D-30623 Hannover, Germany
SO 6th Annual Meeting of the German Society for Clinical Pharmacology and Therapeutics, Dresden, Germany, September 5-7, 1996. European Journal of Clinical Pharmacology 50 (6). 1996. 551. ISSN: 0031-6970
DT Conference
LA English

L7 ANSWER 4 OF 13 BIOSIS COPYRIGHT 1997 BIOSIS
AN 96:210279 BIOSIS
DN 98766408
TI **Lovastatin** enhances the renal microvascular vasodilator response to acetylcholine.
AU Inman S R; Stowe N T; Novick A C
CS Cleveland Clin. Found., Cleveland, OH 44195, USA
SO Experimental Biology 96, Part II, Washington, D.C., USA, April 14-17, 1996. FASEB Journal 10 (3). 1996. A547. ISSN: 0892-6638
DT Conference

LA English

L7 ANSWER 5 OF 13 BIOSIS COPYRIGHT 1997 BIOSIS
AN 96:192528 BIOSIS
DN 98748657
TI Preservation of endothelium-dependent vascular relaxation in cholesterol-fed mice by the chronic administration of prazosin or **pravastatin**.
AU Kamata K; Kojima S; Sugiura M; Kasuya Y
CS Dep. Physiol. Morphology, Inst. Medicinal Chem., Hoshi Univ., Shinagawa-ku, Tokyo 142, Japan
SO Japanese Journal of Pharmacology 70 (2). 1996. 149-156. ISSN: 0021-5198
LA English
AB The relaxation of aortic rings in response to acetylcholine (ACh) was significantly decreased in cholesterol-fed mice. The attenuated relaxation in cholesterol-fed mice was preserved by the chronic administration of prazosin (20 mg/kg/day) or **pravastatin** (12.5 mg/kg/day). Serum low-density lipoprotein (LDL) levels were significantly increased in mice given cholesterol. The increased serum LDL levels in cholesterol-fed mice were returned to normal by the chronic administration of prazosin and **pravastatin**. A prior incubation of aortic rings with lysophosphatidylcholine (LPC) significantly attenuated ACh- and A23187-induced endothelium-dependent relaxation. The inhibitory effects of LPC on endothelium-dependent relaxation were not affected by indomethacin or superoxide dismutase. The sodium nitroprusside-induced relaxation of aortic rings was not changed by LPC. The inhibitory effects on ACh-induced relaxation by N-G-monomethyl-L-**arginine** were restored by a prior exposure to L-**arginine**, whereas the inhibition of endothelium-dependent relaxation by LPC was not affected by L-**arginine**. These results suggest that cholesterol-fed mice are useful animal models of hypercholesterolemia, and chronic administration of prazosin or **pravastatin** can preserve endothelium-dependent relaxation by lowering serum LDL in these animals. It is further suggested that LPC derived from oxidized LDL may be involved in the reduced endothelium-dependent relaxation in hyperlipidemia.

L7 ANSWER 6 OF 13 BIOSIS COPYRIGHT 1997 BIOSIS
AN 96:146796 BIOSIS
DN 98718931
TI Intravenous L-**arginine** restores vascular reactivity in the conduit arteries of young hypercholesterolemic adults.
AU Clarkson P; Henry R; Donald A; Powe A; Bull T; Deanfield J
CS Great Ormond Street Hospital NHS Trust, London, UK
SO 45th Annual Scientific Session of the American College of Cardiology, Orlando, Florida, USA, March 24-27, 1996. Journal of the American College of Cardiology 27 (2 SUPPL. A). 1996. 271A. ISSN: 0735-1097
DT Conference
LA English

L7 ANSWER 7 OF 13 BIOSIS COPYRIGHT 1997 BIOSIS
AN 95:458482 BIOSIS
DN 98472782
TI Vascular function in the forearm of hypercholesterolaemic patients off and on lipid-lowering medication.
AU Stroes E S G; Koomans H A; De Bruin T W A; Rabelink T J
CS Dep. Nephrol. Hypertension, Room F03.226, Heidelberglaan 100, 3584

CX, Netherlands
SO Lancet (North American Edition) 346 (8973). 1995. 467-471. ISSN: 0099-5355
LA English
AB To study whether vascular dysfunction in hypercholesterolaemia is reversible, we investigated patients without overt arterial disease who were taking maintenance treatment for hypercholesterolaemia. Medication was stopped for 2 weeks, reinstituted for 12 weeks, and again stopped for 6 weeks. During both maintenance treatment and the 12 weeks of step-up medication the lipid profile was improved but did not return to normal. Dose-response curves for serotonin-induced vasodilatation, an index of nitric oxide-dependent vasodilatation, showed a comparable and significant rightward shift after a medication-free period of 2 and 6 weeks compared with control subjects, indicating endothelial dysfunction, which was already maximum after 2 weeks. After 12 weeks of lipid-lowering medication, the difference in endothelial function between controls and patients had disappeared. Co-infusion of L-**arginine**, the substrate for nitric oxide synthase, returned the impaired serotonin response during hypercholesterolaemia to normal, but had no effect on this response in, controls or in patients while on lipid-lowering medication. Neither endothelium-independent vasorelaxation, assessed by sodium nitroprusside infusion, nor vasoconstriction induced by the nitric Oxide blocker L-NMMA, were different between controls and patients, whether the latter were on or off lipid-lowering medication. Our results show an L-**arginine**-sensitive, impaired nitricoxide-mediated vascular relaxation of forearm resistance vessels in hypercholesterolaemia which is reproducible, and reversible after short-term lipid-lowering therapy. Demonstration of such changes in this readily accessible vascular bed will allow larger trials assessing vascular function during lipid-lowering therapy to be done.

L7 ANSWER 8 OF 13 BIOSIS COPYRIGHT 1997 BIOSIS
AN 95:265351 BIOSIS
DN 98279651
TI **Simvastatin** Inhibits the Cellular Signaling and Proliferative Action of **Arginine** vasopressin in Cultured Rat Glomerular Mesangial Cells.
AU Ishikawa S-E; Kawasumi M; Saito T
CS Div. Endocrinol. Metabolism, Dep. Med., Jichi Med. Sch., 3311-1 Yakushiji Minamikawachi-machi, Tochigi 329-04, Japan
SO Endocrinology 136 (5). 1995. 1954-1961. ISSN: 0013-7227
LA English
AB The present study was undertaken to determine whether an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, **simvastatin**, modulates the cellular action of **arginine** vasopressin (AVP) in the cultured rat glomerular mesangial cells. AVP increases cellular free calcium ((Ca-2+)-i) in a dose-dependent manner. The 1 times 10-7 M AVP-mobilized (Ca-2+)-i was significantly reduced in the cells pretreated with 1 times 10-6 M **simvastatin**. AVP produced a biphasic change in cellular pH, namely, an early acidification followed by a sustained alkalinization, and the AVP-induced cellular alkalinization disappeared after exposing to **simvastatin**. 1 times 10-7 M AVP activated mitogen-activated protein (MAP) kinase from 15.5-30.4 pmol/mg protein, an effect significantly less in the presence of **simvastatin**. Also, 1 times 10-7 M AVP significantly increased (3H)thymidine incorporation by 1.6-fold, and its incorporation was

totally diminished in cells pretreated with **simvastatin**. The AVP-induced (Ca-2+)-i mobilization and MAP kinase activation were totally restored when cells were preexposed to a mixture of mevalonate and **simvastatin**. (3H)AVP receptor binding was not affected by the **simvastatin** treatment. 1 times 10-7 AVP increased inositol trisphosphate production by 1.8-fold, which was significantly reduced by the presence of **simvastatin**. These results may indicate that nonsterol pathway plays a crucial role in the cellular action of AVP to produce cell growth of glomerular mesangium.

L7 ANSWER 9 OF 13 BIOSIS COPYRIGHT 1997 BIOSIS
AN 95:30939 BIOSIS
DN 98045239
TI The effect of probucol and vitamin E treatment on the oxidation of low-density lipoprotein and forearm vascular responses in humans.
AU McDowell I F W; Brennan G M; McEneny J; Young I S; Nicholls D P; McVeigh G E; Bruce I; Trimble E R; Johnston G D
CS Dep. Med. Biochem., Univ. Wales Coll. Med., Cardiff CF4 4XN, UK
SO European Journal of Clinical Investigation 24 (11). 1994. 759-765. ISSN: 0014-2972
LA English
AB This study investigates the hypothesis that lipid soluble antioxidants may increase the resistance of low-density lipoprotein (LDL) to oxidation and also enhance vascular endothelial responses in humans. In a double-blind parallel group study, 24 hypercholesterolaemic patients, already on treatment with **simvastatin** (20 mg day-1), were randomized to supplementary treatment with probucol (500 mg bd), vitamin E (400 IU daily) or placebo for 8 weeks. Mean serum cholesterol before antioxidant treatment was 7.00 mmol l-1. Resistance of LDL to oxidation by copper was increased by 830% in the probucol group and by 30% in the vitamin E group. However, thiobarbituric acid reacting substances in whole serum were not altered by either antioxidant. Probucol lowered HDL- and LDL-cholesterol levels and increased the QT interval. Forearm vascular responses, as measured by venous occlusion plethysmography, to acetylcholine, glyceryl trinitrate and NG-monomethyl-L-**arginine**, were not significantly changed by antioxidant treatment. Probucol has a major, and vitamin E a minor, effect on LDL resistance to oxidation but neither compound appears to alter forearm vascular responses in vivo.

L7 ANSWER 10 OF 13 BIOSIS COPYRIGHT 1997 BIOSIS
AN 94:518670 BIOSIS
DN 97531670
TI Deceleration by **simvastatin** of **arginine** vasopressin (AVP)-induced cellular growth of the cultured rat glomerular mesangial cells (GMC).
AU Ishikawa S; Kawasaumi M; Okada K; Saito T
CS Dep. Med., Jichi Med. Sch., Tochigi 329-04, JAP
SO Abstracts Submitted for the 27th Annual Meeting of the American Society of Nephrology, Orlando, Florida, USA, October 26-29, 1994. Journal of the American Society of Nephrology 5 (3). 1994. 717. ISSN: 1046-6673
DT Conference
LA English

L7 ANSWER 11 OF 13 BIOSIS COPYRIGHT 1997 BIOSIS
AN 94:172429 BIOSIS

DN 97185429
TI Familial defective apolipoprotein B-100: A review, including some comparisons with familial hypercholesterolemia.
AU Myant N B
CS MRC Lipoprotein Team, Hammersmith Hospital, Ducane Rd., London W12 OHS, UK
SO Atherosclerosis 104 (1-2). 1993. 1-18. ISSN: 0021-9150
LA English
AB Familial defective apolipoprotein B-100 (FDB) is a dominantly inherited disorder caused by the substitution of glutamine for **arginine** at position 3500 in apo B-100. The presence of mutant apo B-100 in low-density lipoproteins (LDL) markedly reduces their affinity for the LDL receptor, leading to hypercholesterolaemia and increased proneness to coronary artery disease. In some FDB heterozygotes the clinical picture is indistinguishable from that in heterozygous familial hypercholesterolaemia (FH). In European and N. American populations the frequency of FDB is at least as high as that of FH. In most lipid clinics, 2-5% of patients given a clinical diagnosis of FH have FDB, not FH. Most FDB heterozygotes respond well to drugs that lower plasma LDL levels by inducing receptor activity. This may be due partly to increased receptor-mediated hepatic removal of mutant and normal precursors of LDL, using apo E as recognition element. Several important lessons can be learnt from the study of FDB.

L7 ANSWER 12 OF 13 BIOSIS COPYRIGHT 1997 BIOSIS
AN 94:123104 BIOSIS
DN 97136104
TI 3-Hydroxy-3-methyl glutaryl coenzyme A reductase inhibition modulates vasopressin-stimulated Ca-2+ responses in rat A10 vascular smooth muscle cells.
AU Ng L L; Davies J E; Wojcikewicz R J H
CS Dep. Pharmacol., Clinical Sci. Build., Leicester Royal Infirmary, Leicester LE2 7LX, UK
SO Circulation Research 74 (2). 1994. 173-181. ISSN: 0009-7330
LA English
AB Previous evidence has indicated a role for changes in cell membrane cholesterol in the modulation of (Ca-2+)-i responses and smooth muscle contraction to vascular agonists. However, the actions of plasma cholesterol-lowering agents such as 3-hydroxy-3-methyl glutaryl coenzyme A reductase inhibitors (eg, **simvastatin**) have not been defined. Such agents may in addition affect isoprenoid intermediates that may play a role in signal transduction pathways involving G proteins. **Arginine** vasopressin-induced (Ca-2+)-i responses in A10 rat vascular myocytes were therefore studied in vitro. Vasopressin stimulated an initial peak (Ca-2+)-i that was independent of extracellular Ca-2+ entry and a subsequent plateau that was dependent on Ca-2+ influx, mainly through receptor-operated dihydropyridine-insensitive divalent cation channels. **Simvastatin**-treated A10 cells (5 mg/L for 24 hours) showed a normal initial peak response to vasopressin, but the plateau phase of Ca-2+ entry was significantly impaired. By use of Mn-2+ quenching of intracellular fura 2 to measure divalent cation entry, the maximal rate of vasopressin-stimulated Mn-2+ entry was impaired in **simvastatin**-treated cells by 52%. Mevalonate (1 mmol/L for 4 hours at 37 degree C) reversed all the changes in **simvastatin**-treated cells. There were no associated changes in total cellular cholesterol or fluorescence anisotropy measurements with **simvastatin** treatment. Measurements of

inositol-1,4,5-trisphosphate mass showed that **simvastatin** did not impair the initial peak response to vasopressin but significantly reduced the subsequent plateau phase. These changes were also reversed with mevalonate incubation. These findings suggest that **simvastatin** has additional effects on (Ca-2+)-i homeostasis that are independent of changes in total cell cholesterol.

L7 ANSWER 13 OF 13 BIOSIS COPYRIGHT 1997 BIOSIS
AN 92:69063 BIOSIS
DN BA93:37518
TI HYPERCHOLESTEROLEMIA AND ATHEROSCLEROSIS CHANGE VASCULAR REACTIVITY IN RABBITS BY DIFFERENT MECHANISMS.
AU GALLE J; BUSSE R; BASSENGE E
CS INSTITUT FUER ANGEWANDTE PHYSIOLOGIE DER UNIVERSITAET, HERMANN HERDER STRASSE 7, D-7800 FREIBURG, WEST GERMANY.
SO ARTERIOSCLER THROMB 11 (6). 1991. 1712-1718. CODEN: ARTTE5 ISSN: 1049-8834
LA English
AB Vasomotor reactivity was assessed in vitro in arterial segments obtained from rabbits with different stages of atherosclerosis. Rabbits were fed a standard chow diet (controls) or a cholesterol-enriched diet to induce hypercholesterolemia and atherosclerosis. A third group received the hydroxymethylglutaryl coenzyme A reductase inhibitor, **lovastatin**, simultaneously with the cholesterol diet. Contractile responses of thoracic aortas to norepinephrine, serotonin, and potassium-rich solution, as well as endothelium-dependent dilations to acetylcholine, were compared after 2 and 4 months on the respective diet. Additionally, plasma cholesterol levels and the amount of plaques covering the intimal surface (as a percentage of the intimal surface) were determined; transmission electron microscopy of atherosclerotic arteries was also performed. After 2 months, the only difference was an enhancement of contractile responses to serotonin in the cholesterol-fed versus the control group. After 4 months on the diet, contractile responses to serotonin were further enhanced, and norepinephrine- and potassium-induced vasoconstrictions were now also significantly enhanced in cholesterol-fed animals versus controls. Endothelium-dependent vasodilations were simultaneously reduced in cholesterol-fed animals. These alterations were partly prevented in cholesterol-fed and **lovastatin**-treated animals. Suppression of nitric oxide synthesis in control aortas by NG-nitro-L-**arginine** did not reveal any significant increases in contractile responses. Contractile responses to serotonin were enhanced after 2 months on the diet but before the appearance of intimal plaques, whereas attenuation of endothelium-dependent dilations, as well as the further enhancement of contractile responses to serotonin and to other agonists, were closely correlated with the degree of intimal plaques after 4 months on the diet. The similarity of alterations in vascular reactivity after 4 months on the diet to the effects of isolated low density lipoproteins on vascular tone and the correlation of these changes with the degree of lipid-containing plaques support the hypothesis that lipoprotein accumulation in atheroclerotic arteries contributes to alterd vascular reactivity.

6 ANSWERS ARE AVAILABLE. SPECIFIED ANSWER NUMBER EXCEEDS ANSWER SET SIZE
ENTER ANSWER NUMBER OR RANGE (1):1-6

L8 ANSWER 1 OF 6 BIOSIS COPYRIGHT 1997 BIOSIS
AN 97:178815 BIOSIS
DN 99470528
TI Protein engineering of the **HMG-CoA** reductase of Pseudomonas mevalonii. Construction of mutant enzymes whose activity is regulated by phosphorylation and dephosphorylation.
AU Friesen J A; Rodwell V W
CS Dep. Biochemistry, Purdue Univ., West Lafayette, IN 47907-1153, USA
SO Biochemistry 36 (8). 1997. 2173-2177. ISSN: 0006-2960
LA English
AB The activity of Pseudomonas mevalonii **HMG-CoA** reductase (EC 1.1.1.88) is not regulated by phosphorylation, presumably due to the absence of a suitable target serine and protein kinase recognition motif. We have engineered P. mevalonii **HMG-CoA** reductase to a form whose activity, like that of mammalian **HMG-CoA** reductases, is regulated by phosphorylation/dephosphorylation. We substituted serine for **arginine** 387, the residue that corresponds to the regulatory serine of the **HMG-CoA** reductases of higher eukaryotes. A recognition motif for cAMP-dependent protein kinase was added by replacing leucine 384 by histidine (enzyme L384H/R387S) and also valine 391 by leucine (enzyme L384H/R387S/V391L). The activity of P. mevalonii **HMG-CoA** reductase mutant enzymes L384H/R387S and L384H/R387S/V391L was attenuated by phosphorylation. Restoration of activity accompanied subsequent dephosphorylation catalyzed by lambda protein phosphatase. Incorporation and subsequent release of phosphate paralleled the attenuation and restoration of catalytic activity. Incorporation of 0.5 mol of phosphate per subunit was accompanied by an approximately 50% decrease in initial activity. As in the analogous Syrian hamster mutant enzyme S871D, P. mevalonii mutant enzyme R387D exhibited 10% wild-type activity, suggesting that the attenuation of activity that accompanies phosphorylation results at least in part from the introduction of negative charge. Engineering of P. mevalonii **HMG-CoA** reductase to forms whose activity is reversibly regulated by phosphorylation/dephosphorylation provides an attractive model for future structure-based mechanistic studies. Solution of the X-ray structure of phosphorylated and dephosphorylated forms of engineered P. mevalonii **HMG-CoA** reductase should then reveal interactions of the active site phosphoseryl residue that result in attenuation of catalytic activity.

L8 ANSWER 2 OF 6 BIOSIS COPYRIGHT 1997 BIOSIS
AN 96:523104 BIOSIS
DN 99245460
TI Modeling of a mutation responsible for human 3-hydroxy-3-methylglutaryl-CoA lyase deficiency implicates histidine 233 as an active site residue.
AU Robert J R; Mitchell G A; Miziorko H M
CS Dep. Biochem., Med. Coll. of Wisconsin, 8701 Watertown Plank Rd., Milwaukee, WI 53226, USA
SO Journal of Biological Chemistry 271 (40). 1996. 24604-24609. ISSN: 0021-9258
LA English
AB 3-Hydroxy-3-methylglutaryl-CoA (**HMG-CoA**) lyase is inactivated by diethyl pyrocarbonate (DEPC); activity can be fully restored by incubation with hydroxylamine. Protection against DEPC inactivation is afforded by a substrate analogue, suggesting an

active site location for a DEPC target. Included in the inherited defects that map within the **HMG-CoA** lyase gene is a point mutation that results in an **arginine** substitution for histidine 233, one of only two invariant histidines. These observations prompted a functional test of the importance of His-233. The mutant lyases H233R, H233A, and H233D were overexpressed in Escherichia coli, isolated, and kinetically characterized. In H233D, DEPC targets one less histidine than was measured using wild-type lyase, supporting the assignment of wild-type lyase His-233 as one of the DEPC targets. Substitution of His-233 results in diminution of activity by apprx 4 orders of magnitude. K-m values of the mutant lyases for both substrate **HMG-CoA** and activator divalent cation (Mg-2+ or Mn-2+) are comparable to the values measured for wild-type enzyme, indicating that these enzymes retain substantial structural integrity. This conclusion is reinforced by the observation that the affinity label, 2-butynoyl-CoA, stoichiometrically modifies the mutant lyases, indicating that they contain a full complement of active sites. In view of these data suggesting that the structures of these mutant lyases closely approximate that of the wild-type enzyme, their observed 10-4-fold diminution in catalytic efficiency supports assignment to His-233 of a role in the chemistry of **HMG-CoA** cleavage.

L8 ANSWER 3 OF 6 BIOSIS COPYRIGHT 1997 BIOSIS
AN 96:514721 BIOSIS
DN 99237077
TI Structural determinants of nucleotide coenzyme specificity in the distinctive dinucleotide binding fold of **HMG-CoA** reductase from Pseudomonas mevalonii.
AU Friesen J A; Lawrence C M; Stauffacher C V; Rodwell V W
CS Dep. Biochem., Purdue Univ., West Lafayette, IN 47907, USA
SO Biochemistry 35 (37). 1996. 11945-11950. ISSN: 0006-2960
LA English
AB The 102-residue small domain of the 428-residue NAD(H)-dependent **HMG-CoA** reductase of Pseudomonas mevalonii (EC 1.1.1.88) binds NAD(H) at a distinctive, non-Rossmann dinucleotide binding fold. The three-dimensional structure reveals that Asp146 lies close to the 2'-OH of NAD+. To investigate the role of this residue in determination of coenzyme specificity, Asp146 was mutated to Ala, Gly, Ser, and Asn. The mutant enzymes were analyzed for their ability to catalyze the oxidative acylation of mevalonate to **HMG-CoA** using either the natural coenzyme NAD+ or the alternate coenzyme NADP+. Mutation of Asp146 to Ala or Gly increased the specificity for NADP+, expressed as the ratio of k-cat/K-m for NADP+ to k-cat/K-m for NAD+, 1200-fold (enzyme D146G) and 6700-fold (enzyme D146A). Mutation of Asp146 was accompanied by 565-fold (DI 46G) and 330-fold (D146A) increases in k-cat/K-m for NADP+ and 2-fold (D146G) and 20-fold (D146A) decreases in k-cat/K-m for NAD+. To further improve NADP+ specificity, Gln147, Leu148, Leu149, or Thr192 of enzyme D146G or D146A was replaced by lysine or **arginine**, which could stabilize the 2'-phosphate of NADP+. Enzymes D146G/T192K, D146G/T192R, D146G/L148K, D146A/L148K, and D146A/L148R exhibited 3200-, 4500-, 56 000-, 72 000-, and 83 000fold increases in the specificity for NADP+ relative to the wild-type enzyme.

L8 ANSWER 4 OF 6 BIOSIS COPYRIGHT 1997 BIOSIS
AN 95:76795 BIOSIS
DN 98091095

TI 3-Hydroxy-3-methylglutaryl-CoA Lyase Is Present in Mouse and Human Liver Peroxisomes.
AU Ashmarina L I; Rusnak N; Miziorko H M; Mitchell G A
CS Service Genetique Medicale, Hopital Sainte-Justine, 3175 Cote Sainte-Catherine, Montreal, PQ H3T 1C5, Canada
SO Journal of Biological Chemistry 269 (50). 1994. 31929-31932. ISSN: 0021-9258
LA English
AB 3-Hydroxy-3-methylglutaryl (**HMG**)-**CoA** metabolism is compartmentalized in mitochondria, endoplasmic reticulum, and peroxisomes. We investigated the subcellular distribution of **HMG-CoA** lyase (HL), which is found principally in mitochondria but in which we observed the potential peroxisomal targeting motif cysteinelysine/**arginine**-leucine at the carboxyl terminus. We used differential and density gradient centrifugation to separate peroxisomes and mitochondria in liver homogenates of outbred CD-1 mice. Peroxisomal fractions contained 6.4% of total HL activity in mouse liver and 5.6% in human liver. Liver peroxisomal HL activity increased 2.3-2.5 times following induction of peroxisomal proliferation by clofibrate administration. Western blotting with anti-human HL antibodies confirmed the presence of immunoreactive HL in peroxisomal fractions. Mouse liver peroxisomal HL is distinct from mitochondrial HL, measuring apprx 2.5 kDa more by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. By fast protein liquid chromatofocusing analysis, the pI of peroxisomal HL is 7.3, in contrast to 6.2 for mitochondrial HL. These results are consistent with noncleavage of the mitochondrial leader peptide in peroxisomal HL. A distinct species of enzymatically active HL exists in peroxisomes and may play a role in **HMG-CoA** metabolism in that organelle.

L8 ANSWER 5 OF 6 BIOSIS COPYRIGHT 1997 BIOSIS
AN 94:230599 BIOSIS
DN 97243599
TI An integrated approach to the selection of optimal salt form for a new drug candidate.
AU Morris K R; Fakes M G; Thakur A B; Newman A W; Singh A K; Venit J J; Spagnuolo C J; Serajuddin A T M
CS Pharm. Dev. Div., Bristol-Myers Squibb Pharm. Res. Inst., New Brunswick, NJ 08903, USA
SO International Journal of Pharmaceutics (Amsterdam) 105 (3). 1994. 209-217. ISSN: 0378-5173
LA English
AB A general method was developed to select the optimal salt form for BMS-180431, a novel **HMG-CoA** reductase inhibitor and a candidate for oral dosage form development, in an expeditious manner at the onset of the drug development process. The physicochemical properties such as hygroscopicity, physical stability of crystal forms at different humidity conditions, aqueous solubility, and chemical stability of seven salts, e.g., sodium, potassium, calcium, zinc, magnesium, **arginine** and lysine, were studied using a multi-tier approach. The progression of studies among different tiers was such that the least time-consuming experiments were conducted earlier, thus saving time and effort. A 'go/no go' decision was made after each tier of testing the salts, thus avoiding generation of extensive data on all available salt forms. The hygroscopicities of all BMS-180431 salts were evaluated at tier 1 and four salts (sodium, potassium, calcium and zinc) were dropped from consideration due to excessive moisture uptake within

the expected humidity range of pharmaceutical manufacturing plants (30-50% R.H. at ambient temperature). The remaining three salts were subjected to the tier 2 evaluation for any change in their crystal structures with respect to humidity and the determination of their aqueous solubilities in the gastrointestinal pH range. The magnesium salt was dropped from further consideration due to humidity-dependent changes in its crystal structure and low solubility in water (3.7 mg/ml at room temperature). **Arginine** and lysine salts, which were resistant to any change in their crystalline structures under extremes of humidity conditions (6 and 75% R.H.) and had high aqueous solubilities (gt 200 mg/ml), were elevated to tier 3 for the determination of their chemical stability. Based on solid state stability of these two salts under accelerated conditions (temperature, humidity, and presence of excipients), consideration of ease of synthesis, ease of analysis, potential impurities, etc., and input from the marketing group with respect to its preference of counter ion species, the **arginine** salt was selected for further development. The number of tiers necessary to reach a decision on the optimal salt form of a compound may depend on the physicochemical properties studied and the number of salts available. This salt selection process can be completed within 4-6 weeks and be easily adopted in the drug development program.

L8 ANSWER 6 OF 6 BIOSIS COPYRIGHT 1997 BIOSIS
AN 89:356419 BIOSIS
DN BA88:48533
TI THE SUBSTRATE AND SEQUENCE SPECIFICITY OF THE AMP-ACTIVATED PROTEIN KINASE PHOSPHORYLATION OF GLYCOGEN SYNTHASE AND PHOSPHORYLASE KINASE.
AU CARLING D; HARDIE D G
CS MRC PROTEIN PHOSPHORYLATION GROUP, BIOCHEM. DEP., UNIV., DUNDEE, UK.
SO BIOCHIM BIOPHYS ACTA 1012 (1). 1989. 81-86. CODEN: BBACAQ ISSN: 0006-3002
LA English
AB In addition to acetyl-CoA carboxylase and **HMG-CoA** reductase, the AMP-activated protein kinase phosphorylates glycogen synthase, phosphorylase kinase, hormone-sensitive lipase and casein. A number of other substrates for the cyclic AMP-dependent protein kinase, e.g., L-pyruvate kinase and 6-phosphofructo-2-kinase / fructose-2,6-bisphosphatase, are not phosphorylated at significant rates. Examination of the sites phosphorylated on acetyl-CoA carboxylase, hormone-sensitive lipase, glycogen synthase and phophorylase kinase suggests a consensus recognition sequence in which the serine residue phosphorylated by the AMP-activated protein kinase has a hydrophobic residue on the N-terminal side (i.e., at -1) and at least one **arginine** residue at -2, -3 or -4. Substrates for cyclic AMP-dependent protein kinase which lack the hydrophobic residue at -1 are not substrates for the AMP-activated protein kinase.